INVOLVEMENT OF THE MEDIAL THALAMUS

IN

MULTIPLE ATTRIBUTES OF MEMORY

A thesis

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Abstract

It is widely regarded that the amnesic deficits associated with diencephalic amnesia and medial temporal lobe amnesia are similar. However, the neural basis of diencephalic amnesia and the contributions of different medial thalamic nuclei continue to prove a contentious issue. Contrary to the view that specific medial thalamic nuclei are responsible for profound amnesia after diencephalic injury in humans, the neural connections associated with three aggregates of thalamic nuclei suggest that they each contribute to independent memory systems. These three aggregates were identified by a review of the neuroanatomical tracing studies from the research literature. One thalamic aggregate comprised of the anterior thalamic nucleus (AT), while the other two consisted of less conventional groupings of medial thalamic nuclei, namely a lateral thalamic group (LT) and a posteromedial thalamic group (MT). The LT aggregate was identified as the rostral intralaminar nuclei (paracentral, centrolateral, and rostral central medial) and the lateral and paralamellar segments of the mediodorsal thalamic nucleus. The MT aggregate was identified as the central and medial segments of the mediodorsal nucleus as well as the intermediodorsal nucleus. The functional contributions to specific attributes of memory were assessed in rats across a variety of behavioural tasks. Highly localised lesions to the MT produced deficits on a reward magnitude task, which previously has been found to be sensitive to amygdala and lateral prefrontal lesions, which supports the view that the MT contributes to an amygdala-based memory system. Only AT lesions produced deficits in spatial memory tasks, which are also sensitive to hippocampal lesions, which confirms earlier evidence that the AT contributes to an extended hippocampal system responsible for spatial memory processing. Only LT lesions produced deficits in an egocentric response memory task, which is also disrupted by dorsomedial prefrontal cortex and dorsal striatum lesions, and which thus supports the notion that the LT is a functional component of a dorsal striatum memory system. In addition, LT and MT lesions, but not AT lesions, impaired temporal order memory, while no lesion impaired object recognition or sustained attention. These new dissociations indicate that distributed neural circuits incorporating many brain structures including the medial thalamus can be identified as contributing to independent learning and memory processes.

Chapter 1

Introduction

1.1 General Introduction

It is widely known that learning and memory processes are associated with the medial temporal lobes and hippocampus of the brain (Broadbent et al, 2002; Eichenbaum & Cohen, 2001); there is substantial research and knowledge about memory and deficits associated with these regions. It is also widely known that intact medial diencephalic structures are important for normal learning and memory (Aggleton & Brown, 1999; Kopelman, 2002; Mair, 1994; Zola-Morgan & Squire, 1993) but there is substantially less research and knowledge about memory and deficits related to these regions. Additionally it is now recognised that the episodic memory processes that are disrupted in anterograde amnesia probably involve interactions between the medial temporal lobes and medial diencephalon forming an interconnected circuit first identified by Papez (1937, cited in Aggleton & Brown, 1999). Therefore in order to more fully understand the brain's involvement in processing information successfully and recalling and / or recognising it again, it is paramount that the discussion of anterograde amnesia should not focus only on the medial temporal lobes and hippocampus.

In humans, diencephalic amnesia is associated with alcoholic Korsakoff syndrome, cysts and tumours surrounding the third ventricle of the brain, and infarcts or vascular accidents that cause brain damage in the medial thalamus of the diencephalon (von Cramon et al, 1985; Dusoir et al, 1990; Kopelman, 1995; Markowitsch, 1982; Mair et al, 1979; Parkin et al, 1994; van der Werf, Witter, Ulyings, & Jollie, 2000; Victor et al, 1989; Schmahmann, 2003). Recently it has also been proposed that some of the neuropsychological impairments associated with variant Creutzfeldt-Jakob disease, which impairs the ability to retain new episodic information and retrieve information from semantic memory and general public knowledge, and diminishes executive functioning, are the result of damage in the dorsal thalamus and dorsal striatum (Kapur et al, 2001; Kapur et al, 2003).

Unfortunately, the thalamic brain injury that occurs in human cases is often highly variable and has not, to date, been consistently linked to just one specific diencephalic structure or nucleus in the medial thalamus. Therefore, there remains no definitive answer to the neural basis of diencephalic amnesic deficits. Nevertheless, clinical evidence, based on neuropathological studies and neuronal imaging techniques (Aggleton & Sahgal, 1993; Aggleton & Saunders, 1997; Harding et al, 2000; Kopelman et al, 1997, 1999; Van der Werf et al, 2003a), as well as animal lesion models, implicates the mediodorsal, anterior, intralaminar, midline thalamic nuclei or either one of two fibre pathways, the internal medullary lamina or the mammillothalamic tract of the medial diencephalon (Aggleton & Brown, 1999; Gaffan & Parker, 2000; Mair, 1994; Mennemeier et al, 1992; Parker & Gaffan, 1997; Victor et al, 1989; van der Werf et al, 2000; 2003b). For example, it was recently theorised that the anterior thalamic nuclei (AT), an important group of diencephalic structures, plays an essential role in learning and memory processes. Aggleton and Brown (1999) recently summarised the relevant human and animal literature and proposed that interactions between parts of the medial diencephalon, especially the AT, and the hippocampal formation support the existence of an 'extended hippocampal system', which reflects the neural circuitry shared by these structures. Moreover this group has suggested that the AT may constitute a pivotal or nodal point within this 'extended hippocampal system' that processes information specific to spatial and context-dependent memory in animals or the relative equivalent, episodic declarative memory in humans (Aggleton & Sahgal, 1993). Research from our behavioural neuroscience laboratory at the University of Canterbury has also confirmed that the AT does indeed play a role in spatial memory in rats (Byatt & Dalrymple-Alford, 1996; Mitchell, Dalrymple-Alford & Christie, 2002; Moran & Dalrymple-Alford, 2003).

Additionally, Aggleton and Brown (1999) suggest that other medial diencephalic structures, particularly the mediodorsal thalamic nuclei (MDn), and the perirhinal cortex of the medial temporal lobe, may play a role in a separate system responsible for familiarity-based recognition processes. However, this proposal remains controversial (e.g. see Markowitsch, 1999; Parker, 1999; Witter & Van der Werf, 1999) because the direct neural connections between the MDn and perirhinal cortex are very sparse and clinical and animal lesion evidence remains equivocal.

In contrast to this latter proposal Parker and colleagues have proposed that the MDn, in particular the magnocellular subdivision of the mediodorsal nucleus in monkeys, also has an important integrative role in conjunction with the prefrontal cortex (PFC) in

episodic-like declarative memory, due to the prominent interconnections between the MDn and the PFC (Gaffan & Parker, 2000; Parker, 1999; Parker et al, 1997). Yet, in contrast to this notion other researchers have proposed that the MDn has a deferential role in memory processing that is in some way related to disruptions in executive functioning, which are proposed to be processed by the PFC. For example, it has been suggested that the memory impairments resulting from lesions to the MDn are secondary to the primary disruptions in executive functioning, e.g. deficits in attention or withholding responses / inhibition and perseverative responding in both humans and animals (Alexinsky, 2001; Hunt & Aggleton, 1998a, b; Savage et al, 1999; Schmahmann, 2003; Van der Werf et al, 2000, 2003; Zola-Morgan & Squire, 1985).

In contrast to the above proposals of the neural basis of thalamic amnesia, other researchers (Mair, 1994; Mair et al, 1998, 1999; Savage et al, 1997, 1999; Young et al, 1996) have highlighted the importance of the midline and intralaminar (ILn) thalamic nuclei, another important group of medial diencephalic structures, and propose these nuclei play an essential role in learning and memory processes. It has been proposed that the ILn participate in memory processing by interacting with cortical and striatal components of basal ganglia–thalamo–cortical pathways (Alexander et al, 1986; Berendse & Groenewegen, 1990, 1991; Groenewegen & Berendse, 1994) and that amnesia associated with ILn lesions are functionally distinct from amnesia associated with hippocampal or prefrontal cortical pathology. Additionally, ILn lesions thus far reported in the animal literature are associated with delay-independent deficits, which may indicate that the impaired memory processing associated with ILn lesions is secondary to other behavioural deficits associated with perception or maintaining attention (Mair et al, 1998; Savage et al, 1999).

Gabriel's (1993) theory offers another alternative to the proposal of Aggleton and Brown (1999). Gabriel reports that the AT and MDn and their respective cortical networks (posterior and anterior cingulate cortical areas, respectively) act in a cooperative manner during learning but are differentially involved during the acquisition and maintenance of learned behaviour. For example, the system comprising of the MDn and anterior cingulate cortex is proposed to be involved in the initial stages of learning, while electrophysiological changes in neuronal activity in the AT and posterior cingulate cortex system are not observed until late in training, suggesting that this system is involved in the maintenance of the learned acquisition even after more recent information has been

obtained (Gabriel, 1993). Gabriel does not include a role for the ILn or midline thalamic nuclei in his theory.

Thus, research and knowledge has emerged implicating individual regions of the medial diencephalon in learning and memory processes. However, identifying the fundamental region responsible for diencephalic amnesia remains to be determined.

1.2 Aims of the Present Study

As the above brief introduction indicates the neural basis of thalamic amnesia remains a contentious issue. While it is known that damage in the medial thalamus causes memory impairment, it is still not known what role(s) the medial thalamus contributes to memory processes. Patients with brain injury sustained in the medial thalamus can suffer from severe memory deficits, which will differ across individuals in both variability and magnitude of disruptions. Diencephalic amnesics can also suffer deficits in attention and problems with executive functioning. However, the critical locus of the memory deficits and / or attentional and executive functioning deficits remains uncertain. Thus far, human cases of diencephalic amnesia with damage limited to the thalamus have resulted in disruptions to more than one medial thalamic nucleus or grouping of nuclei, so the human literature is unlikely to provide conclusive evidence.

Animal lesion models causing damage to the medial thalamus have been promising but are wrought with many methodological issues. To date lesions produced in animals have more often than not been too large, resulting in damage that is not sufficiently restricted to just one group of nuclei. Likewise in the case of the animal pyrithiamine induced thiamine deficiency model of Wernicke's encephalopathy / Korsakoff syndrome, differences in the extent and dosage of treatment have been variable across studies offering little further insight into examples of thalamic amnesia. Furthermore, all three medial thalamic groupings of nuclei, that is the AT, MDn and ILn have not been assessed within the same experiments using the same tasks, and experimental designs. Functional dissociations even between the AT and MDn have seldom been examined.

The contribution of the present study was to focus on the different thalamic nuclei implicated in memory processes and position them within functionally segregated circuits, all responsible for memory processing carried out by the brain, albeit for different attributes of memory. This hypothesis, then, challenges or extends the present theories about memory processes and deficits related to the medial thalamus.

There were several aims of the present study. A reassessment of the most significant neural connections of the medial thalamus was essential, so that the common aggregates of medial thalamic nuclei could be positioned amongst widely identified parallel neural circuits operating as a whole to process information. Secondly, highly selective lesions were achieved in these medial thalamic aggregates to ensure a reliable assessment of behavioural and memory functions. Direct behavioural comparisons were then made of individual aggregates of medial thalamic nuclei using restricted lesions across an array of memory tasks so that if double dissociations exist, they may be more readily identified. While double dissociations and interactions do not provide 'magic bullets', they still prove useful in providing good constraints on current theories and allow re-evaluations not solely based on correlational relationships (Baddeley, 2003).

Therefore the methodological requirements of this thesis were to produce highly selective lesions to the independent aggregates of the medial thalamus identified from the re-assessment of the significant neural connections, and once achieved, rats were tested with these lesions on a range of memory processing tasks, in order to draw conclusions on the likelihood that each of the medial thalamic nuclei contribute to specific forms or different attributes of memory.

As will be shown, the neural connections of the medial thalamus indicate three aggregates of thalamic nuclei. One aggregate involving the anterior thalamic nuclei (AT), one comprising of the lateral medial thalamic nuclei (LT) and one comprising of the posteromedial thalamic nuclei (MT). The assessment of behavioural studies included both memory and attention tasks, which have previously demonstrated reliable assessments of both memory and other behavioural impairments following lesions in the rat.

These memory impairments and dissociations (both single and double) support the work of some previous studies of memory related deficits in the medial diencephalon, while at the same time offering many novel findings. Therefore, re-interpretations of the research literature are required in order to provide a better understanding about the memory deficits suffered following damage in the medial thalamus.

1.3 Outline of thesis

The following chapter provides an introduction to the medial thalamic nuclei of interest in the current thesis; it covers the basic anatomy, morphology and connectivity of these nuclei. The subsequent three chapters discuss the theoretical views about memory and the

brain. Chapter Three reviews the memory theories that have focused mainly on the temporal lobes and hippocampus. Both dual-process and multiple memory systems theories are discussed, and one of these theories, the Multiple Attribute model of Memory (Kesner & DiMattia, 1987), in particular is highlighted in further detail, as it provides the basis for the behavioural evaluations about memory processes carried out by the medial diencephalon. In Chapter Four, the focus switches to an introduction to diencephalic amnesia and an in depth review of clinical cases that have used brain imaging techniques and neuropathology to elucidate the neural basis of the amnesic syndromes. In Chapter Five, animal models of memory deficits associated with medial thalamic lesions are reviewed.

The framework of the current research is laid out in Chapter 6 by providing evidence about the neural connections of the medial thalamus. The theories of multiple attributes of memory are re-examined and examples of behavioural tasks (from the animal lesion literature) are briefly reviewed that have been used to highlight the notion that different brain regions interconnected with the three independent medial thalamic aggregates are involved in different attributes of memory.

Three further chapters (7-9) present individual sets of experiments that were undertaken in this thesis. Each of the studies employed highly selective N-methyl-D-aspartate acid lesions to individual target nuclei in order to establish whether they process information in similar ways to their neuroanatomically connected structures and investigate whether some interactions and dissociations exist amongst the medial thalamic nuclei on an array of different memory tasks. Chapter Seven investigated memory impairments following lesions to the AT, LT and MT on spatial working and reference memory, memory for temporal order, memory for familiarity versus novelty object recognition and memory for magnitude of reward value. Chapter 8 investigated memory impairments following lesions to the AT and LT on acquisition of spatial memory and working memory for an egocentric response. Chapter 9 investigated LT and MT lesions on post-operative performance of a sustained attention (vigilance) task and memory for temporal order and memory for familiarity versus novelty object recognition.

The dissertation is discussed in Chapter 10 and indicates the behavioural and theoretical contributions of the current research to our knowledge about the neural basis of medial thalamic amnesia and memory processes of the brain in general. Some suggestions are also made about future directions for the research.

Chapter 2

Location, Morphology and Basic Connectivity of the Medial Thalamus

2.1 Introduction

The thalamus forms part of a collective group of brain structures referred to as the diencephalon (between brain), other structures include the hypothalamus, and sub-thalamic nuclei. The diencephalon is located within the forebrain, centred subcortically between the two frontal lobes and within the region of the third ventricle. The thalamus itself is an ovoid structure (in humans) that consists of a large number of nuclei. There is a thalamus in each hemisphere of the brain and these two regions are connected in the middle of the brain by the massa intermedia and by some of the midline nuclei of the thalamus itself.

The specific thalamic nuclei of interest in the present thesis are located in the medial thalamus, namely the anterior (AT), mediodorsal (MDn), intralaminar (ILn) nuclei, and some of the rostral midline thalamic nuclei. All of these structures (as well as ventral medial nuclei and medial pulvinar) are located between the thalamic midline and, in the rostral medial thalamus, the reticular thalamic nucleus, while in the caudal medial thalamus, the lateral border of the internal medullary lamina (Jones, 1985). This group of structures (along with the laterodorsal thalamic nucleus) are also referred to as the 'limbic thalamus' due to their connections with the limbic system of the brain, e.g. the cingulate / retrosplenial cortex, the medial temporal lobe structures, amygdala and septal area (Bentivoglio et al, 1993). In addition, many different fibre tracts also surround or traverse the medial thalamus connecting the various thalamic nuclei with other cortical and subcortical structures, including the mammillothalamic tract, internal medullary lamina, the fornix, and the amydalofugal pathway (see Figs. 1 & 2).

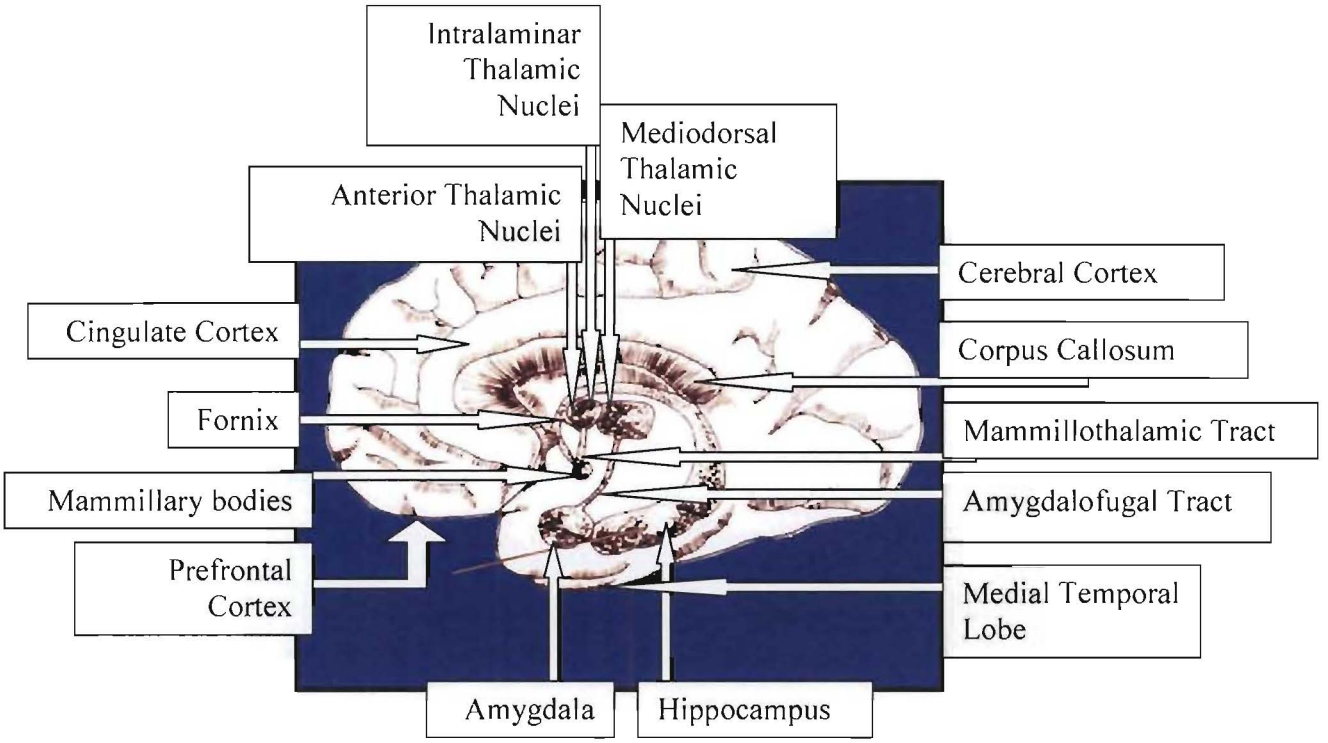

Fig 1. Lateral View of the Human Brain

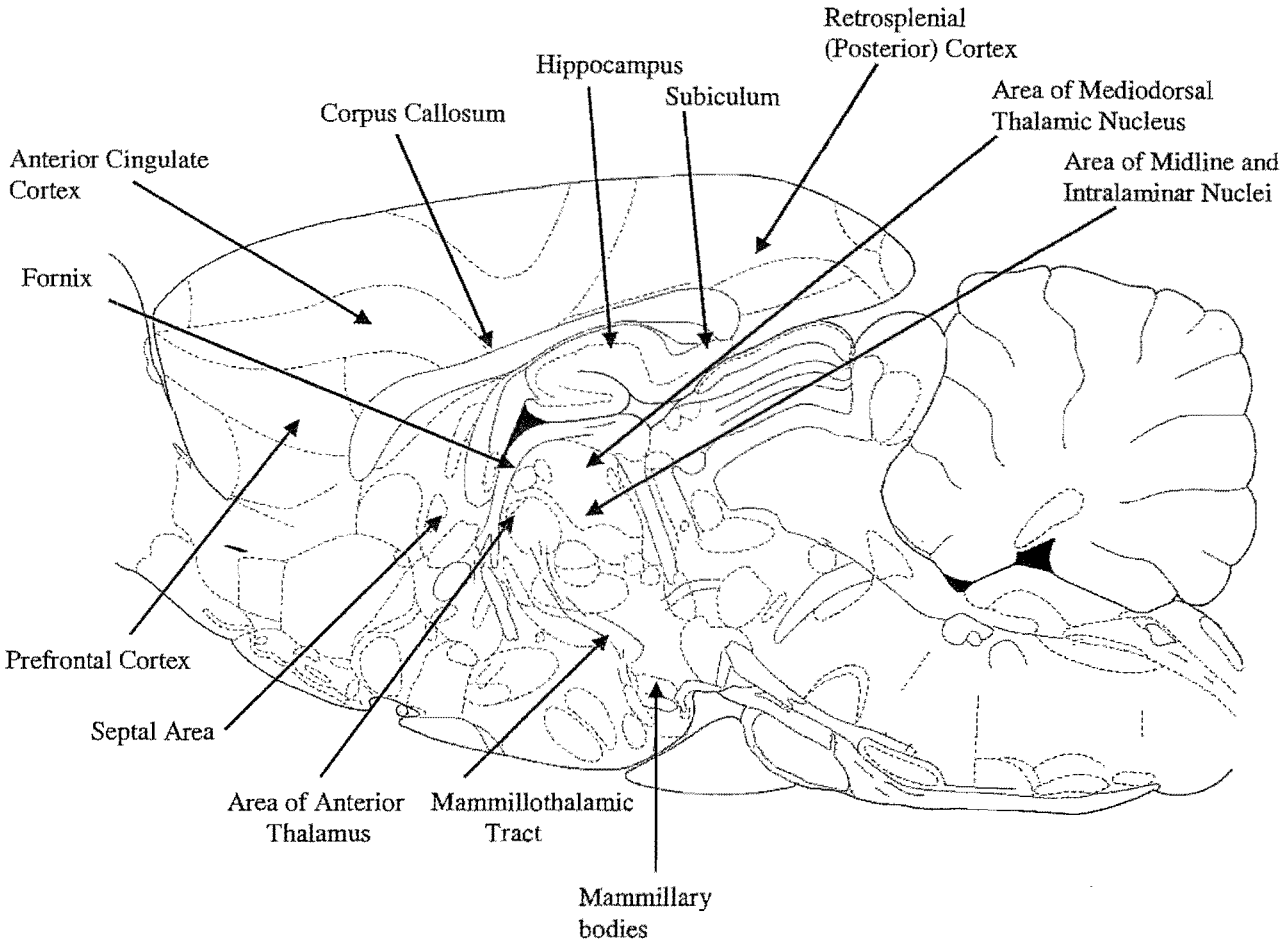

Fig 2. Lateral View in the midsagittal plane of the Rat Brain and Major Structures

Relatively little research has investigated the functioning of the medial thalamus, in sharp contrast to other regions of the brain, for example the hippocampus (Eichenbaum & Cohen, 2001). This lack of research has mainly been due to the widely regarded proposal that the thalamus operates as the central relay station of the brain, simply transmitting information between other sub-cortical structures and cortical areas (Jones, 1985; Price, 1995). Thus, memory deficits resulting from thalamic injury were not considered to be due to a functional role of the thalamus in memory processes itself but rather due only to a loss of information flowing between other brain regions involved in memory (Macchi, 1997).

Alternatively, the thalamus has been considered important for cognitive and emotional or affective and visceral functions to some degree through its involvement with prefrontal cortex connections (see Alexander et al, 1986; Groenewegen et al, 1990). According to this latter notion the memory deficits associated with thalamic injury represent 'frontal lobe amnesia'; clinical cases of thalamic amnesia present with symptoms similar to the dysexecutive functioning syndrome (Baddeley & Warrington, 1973) and deficits in memory processing are considered to be the result of a loss of frontal lobe regulation (Van der Werf et al, 2000, 2003a, b).

More recently, research has suggested that the medial thalamus contributes a functional role to the information that it receives. Animal research especially has provided evidence that suggests the nuclei of the medial thalamus processes and adds to the information that it transmits, forming a critical component within information processing systems of the brain. This suggests that the memory deficits associated with thalamic injury are the consequence of a pure memory disorder, whereby the medial thalamic nuclei are central structures involved in memory processes operating in a similar manner to the structures of the medial temporal lobes (Aggleton & Brown, 1999).

The hypotheses incorporated into this latter notion provide the impetus for the current research. As yet the neural basis of thalamic amnesia remains unresolved. Clinical evidence following medial thalamic injury still remains inconclusive with respect to the contributions of individual thalamic nuclei to memory and other cognitive and behavioural impairments (Schmahmman, 2003; Van der Werf et al, 2003a, b). Animal research has made some progress into establishing the types of information processed by the AT, ILn and MDn thalamic nuclei, but the results are far from conclusive. Therefore our understanding of the neural basis of memory processes related to the thalamus remains an unanswered question.

The following descriptions provide an introduction to the basic anatomy, morphology and connectivity of the particular medial thalamic nuclei of interest in the current research, which aims to determine the neural basis of thalamic amnesia (an extensive review of the neural connections is provided in Chapter 6).

2.2 The Anterior Thalamic Nucleus (AT)

The anterior thalamic nucleus as its name suggests is situated towards the front of the thalamus. It consists of three subdivisions, which are the anteroventral (AV), anteromedial (AM) and anterodorsal (AD) nuclei (Fig. 3A on p. 16). The AD nucleus is the smallest of the three sub-nuclei and has a very distinct cytoarchitecture: it has small, densely packed and darkly stained cells in Nissl-stained preparations. The AD is clearly delineated in the dorsolateral aspect from the AV nucleus by a fibre lamina. The AV is composed of slightly lighter stained, less densely compacted cells. The AV is also distinguished by its remarkably dense concentration of acetylcholinesterase (Price, 1995). The AV merges with the AM, ventromedially. The AM nucleus has larger, paler stained cells that are less well delineated from other adjacent nuclei. In addition, the AM continues across the midline as the interanteromedial nucleus (IAM) and is further characterized by the presence of fibres of the mammillothalamic tract (MMT), which enters ventrolaterally (Bold et al, 1984). In rats, the AM and AV nuclei are of comparable size, clearly separated and cytoarchitecturally distinct (Jones, 1985). In primates, the cytoarchitectonic differences are more subtle and the boundary between AM and AV is difficult to recognise, therefore the term 'anterior principal nucleus' has been designated to the AM-AV complex in primates (Bentivoglio, Kultas-Ilinsky & Ilinsky, 1993).

The AT forms part of an anatomical circuit, identified by Papez (1937; cited in Aggleton & Brown, 1999), which also includes the hippocampal formation, mammillary bodies and cingulate / retrosplenial cortices; it was originally suggested that the circuit processes emotional experiences. This early notion of functionality has since been abandoned and replaced by the proposal that it is primarily involved in mnemonic functions (Aggleton & Brown, 1999). Anatomical knowledge about the Papez circuit has also been refined. The AT receive a heavy bilateral input from the hippocampal formation, either directly via the subicular complex coursing through the fornix (Aggleton et al, 1986; Swanson & Cowan, 1977) or indirectly via a relay through the mammillary bodies (Shibata, 1992). The major cortical targets of the AT are the cingulate cortex and

retrosplenial cortex, plus other significant connections back to the subicular complex that influence hippocampal function (Amaral & Price, 1995). This neural circuit recently referred to as 'the extended hippocampal system' (Aggleton & Brown, 1999) represents a prominent system of connections within the brain.

2.3 The Mediodorsal Thalamus (MDn)

The mediodorsal thalamus is considered the largest of the nuclear structures in the medial thalamus, and it is most developed in primates, especially humans. The increase in the size of the MDn in phylogenetic evolution parallels that of prefrontal associations and cingulate cortices (Bentivoglio et al, 1993). In rats, the MDn is relatively heterogeneous, but four main subdivisions have been identified; these are the medial, central, lateral and paralamellar segments (Groenewegen, 1988; Krettek & Price, 1977; Ray & Price, 1992; see Fig. 3B and 3C on p. 16). The boundaries of each segment are relatively well defined, especially between the central and lateral segments. The dendrites of the cells in each of these two segments tend to be confined to their respective regions and the lateral segment stains more heavily for acetylcholinesterase (Price, 1995). In primates, the four subdivisions are more easily recognisable: a magnocellular subdivision occupies the most medial and anterior part of the MDn and is considered equivalent to the medial segment in rats. The other three subdivisions, parvocellular, pars multiforms, and densocellular are located more laterally. The densocellular subdivision is the most lateral and is difficult to differentiate from the central lateral nucleus of the intralaminar nuclei that borders it anterolaterally (Bentivoglio et al, 1993; Jones, 1997).

The MDn receives inputs from the ventral forebrain regions, association cortex of the temporal lobes, amygdala, and especially dense inputs from frontal cortical areas. The major outputs of the MDn are to the medial prefrontal and insular cortices, and in some neuroanatomical tracing studies in rats the medial prefrontal cortex is said to be defined by the projections received from the MDn nucleus (Groenewegen, 1988; Negyessy et al, 1998) but also see (Kesner, 2000). Other efferent projections of the MDn course to the striatum.

2.4 The Intralaminar Thalamic Nuclei (ILn)

The ILn are an aggregation of cells embedded in and around the internal medullary lamina (IML). There are two sub-groupings: a rostral group and a caudal group. The rostral group consists of the central medial (CeM), central lateral (CL), and paracentral (PC) nuclei. The caudal group, in most species including primates consists of two different nuclei, the parafascicular (Pf) and centre-median (CM) nuclei, referred to as the centre-median-parafascicular (CM-Pf) complex in primates (Groenewegen & Berendse, 1994). In other species including rats, the two nuclei appear as a single mass labelled only the Pf (Van der Werf et al, 2002). The CM is of significant size in primates, especially humans, whereas in other species it is quite small or unidentifiable.

The ILn wrap around the lateral, ventral, and medial borders of the MDn. The anterior extremity of the rostral group of nuclei also lies between the posterior, and medial borders of the AT. The cells of the rostral ILn are large and show deep staining using Nissl techniques. The CeM nucleus is the most ventral of the rostral ILn, and its cells merge at the midline with the same structure in the opposite hemisphere. The CeM extends in a dorsolateral direction along the IML to join the PC nucleus. The PC is mainly located in the anterior and medial parts of the fibre bundle, while the CL comprises the more lateral and posterior position (Fig. 3B and 3C).

Traditionally the ILn and midline (for details see below) thalamic groups have been referred to as non-specific because they were considered to exert a global influence on cortical functioning, previously being described as 'diffuse and non-specific' (Van der Werf et al, 2002). Recently, this notion has been challenged by more refined tracing techniques that have aided neuroanatomical and behavioural investigations. The ILn receive dense inputs from the brainstem reticular formation and are interconnected with the basal ganglia and cerebral cortex.

In the current research, the analyses of memory functioning of the ILn are restricted to the rostral group of nuclei; the caudal group of nuclei are not currently considered memory related structures (Mennemeier et al, 1997; Van der Werf et al, 2002). Atrophy in the caudal group of ILn is associated with Parkinson's disease (Tekin & Cummings, 2002).

2.5 Other medial thalamic nuclei of interest

Other nuclei within the medial thalamus that receive mention in this thesis are the lateral dorsal nucleus and midline nuclei. The midline nuclei are located throughout the dorsal–

ventral continuum of the medial thalamus and include in the dorsal aspects, the intermediodorsal, paraventricular, parataenial nuclei and, in the ventral aspects, the rhomboid and reuniens nuclei.

The laterodorsal (LD) nucleus is considered to be part of the lateral nuclear complex also comprising the lateral posterior (LP) nucleus (see Fig 3A and 3B). It borders the AT posterolaterally and extends caudally throughout the thalamus in its dorsolateral position to the level of the fasciculus restroflexus (fr; see Fig. 3C). It has medium-sized fusiform neurons. The LD is surrounded by a thin fibre capsule that facilitates its identification in all species (Bentivoglio et al, 1993). The LD can be divided two sub-nuclei. The dorsomedial nuclei (LDDM) is located more medially and the ventrolateral nuclei (LDVL) is located more laterally.

Jones (1985) linked the LD along with the AT into a single anterior thalamic nuclei complex, because these nuclei lie adjacent to each other and share many of their cortical projection fields. Therefore, like the AT, the medial LD receives a major input from the hippocampal formation, which courses ipsilaterally via the fornix and indirectly via the internal capsule (Aggleton et al, 1986; Meibach & Siegel, 1977). The LD also sends projections to the retrosplenial cortex and subicular complex (Shibata, 1993; van Groen & Wyss, 1990b). However, unlike the AT, the LD does not receive input from the mammillary bodies. The LD (and LP) also has dense connections with visual related structures, including the superior colliculus, pretectal nuclei and the ventral lateral geniculate nucleus, and there are also extensive connections with both the primary and secondary visual cortical areas (van Groen & Wyss, 1992; Price, 1995). The LD may provide a pathway for sensory information to reach the limbic system (van Groen & Wyss, 1992).

The intermediodorsal nucleus (IMD) is located in between the left and right MDn (see Fig. 3B). In some species it is not recognisable and it is often considered to be part of the medial segment of the MDn (Jones, 1985). The paraventricular (PV) nucleus consists of small densely packed neurons; it is located under the ependyma of the third ventricle and extends throughout the extent of the ILn and midline thalamic nuclei (see Fig. 3A and 3B). The parataenial (PT) nucleus is located in the anterior half of the dorsal thalamus, lateral to the anterior PV (see Fig. 3A). The PT is cytoarchtectonically similar to the medial part of the MDn in rats and terminates posteriorly by fusing with it. The relative size of the PT decreases with phylogenetic evolution so that in higher primates, including humans, this nucleus is represented by a thin band of cells on the anterior and dorsal aspects of the ILn

and MDn nuclei (Bentivoglio et al, 1993). The rhomboid (Rh) nucleus, positioned on top of the reuniens (Re) are located in the ventral aspects of the midline nuclei, beneath the CeM and between the subnuclei (also referred to as the gelatinous nuclei). The Re is subdivided into dorsal Re and ventral Re (see Fig. 3A and 3B). The many midline nuclei are connected with various other structures throughout the brain, which are described in Chapter 6.

Finally, the reticular nucleus (Rt) is introduced here because of its significant interconnections with all medial thalamic nuclei. The Rt is a relatively thin expanse of cells that surround the medial thalamus on its rostral and lateral sides, and the internal capsule surrounds the Rt (see Fig. 3A). All of the medial thalamic nuclei are interconnected with the Rt. Each thalamic nucleus is connected to a restricted sector of the Rt, in the region where it enters and exits the thalamus, and this sector in turn projects fibres back to the same nucleus (Price, 1995). The Rt nucleus regulates the GABA-ergic fibres within the thalamus (Jones, 1985). Although earlier tracing studies suggested that the anterior nucleus were not interconnected with the Rt, more recent studies have provided clear evidence that it is (Shibata, 1992; Sikes & Vogt, 1987). The brainstem and basal forebrain substantially innervates the Rt, with many of these neurons being cholinergic from the LDTg and PPT of the brainstem and GABA-ergic from the basal forebrain.

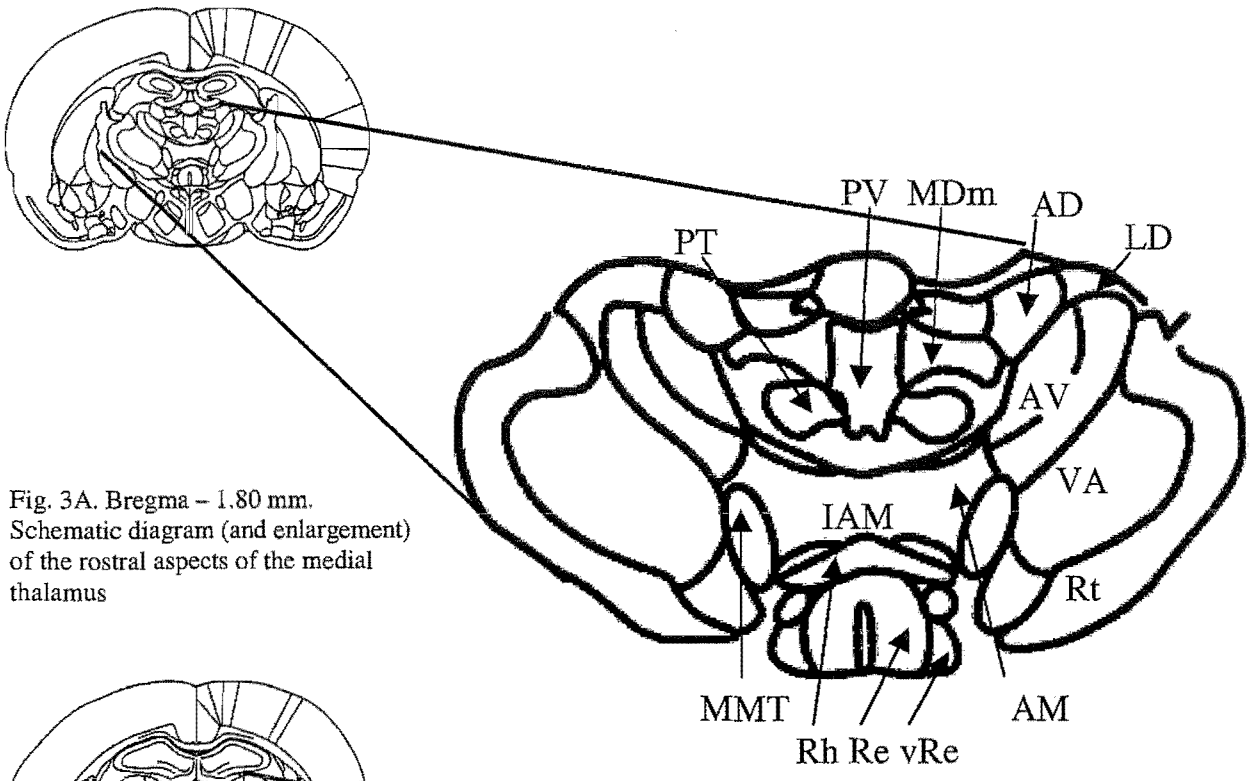

Fig. 3A. Bregma – 1.80 mm. Schematic diagram (and enlargement) of the rostral aspects of the medial thalamus

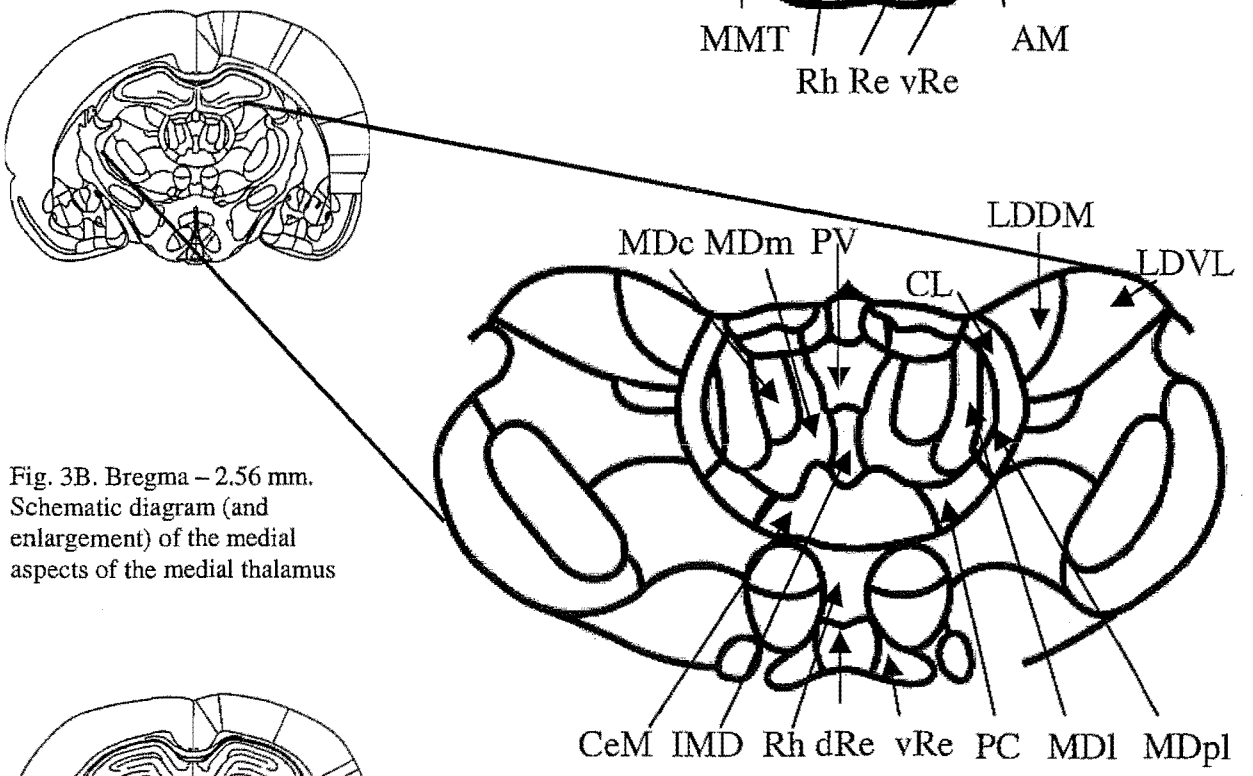

Fig. 3B. Bregma – 2.56 mm. Schematic diagram (and enlargement) of the medial aspects of the medial thalamus

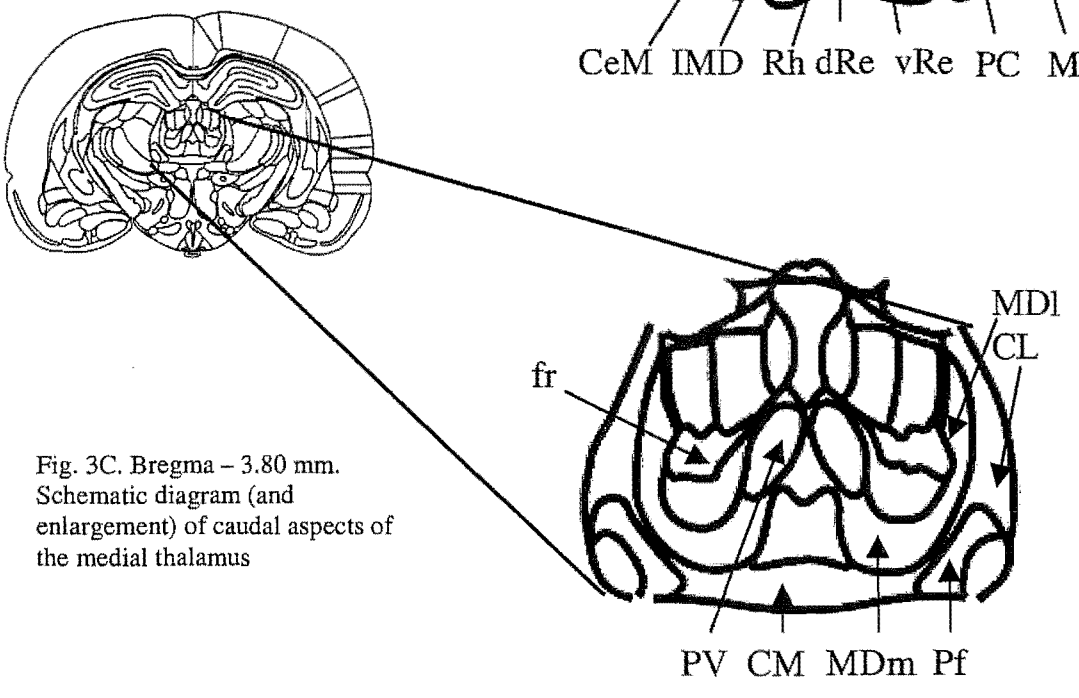

Fig. 3C. Bregma – 3.80 mm. Schematic diagram (and enlargement) of caudal aspects of the medial thalamus

Chapter 3

Human and Animal Amnesia and Memory Systems

This current chapter sets the scene in relation to studying memory and the brain. The initial breakthroughs on memory research are briefly reviewed. Then the main theories proposed about memory and the brain from both human clinical cases and animal lesion models of amnesia are discussed, in particular the memory theories proposed by Squire (1992) and Cohen and Eichenbaum (1993; Eichenbaum & Cohen, 2001), and the parallel multiple memory systems theories proposed by White and McDonald (2002). An alternative to these theories is introduced, the Multiple Attribute Model of Memory proposed by Kesner (1998). As indicated by the obvious exclusions from the list above, this chapter focuses mainly on memory theories related to the hippocampus and medial temporal lobes of the brain. Theories about the involvement of the medial thalamus in memory are discussed in greater detail in Chapter 4, including in particular the proposals of Aggleton and Brown (1999). The chapter concludes with a brief discussion of a relatively recent theory about memory, which refutes the idea of memory systems (Gaffan, 2002; Parker & Easton, 2003).

3.1 The Medial Temporal Lobes and Amnesia

Functional MRI, CT scans, and neuropathological evidence from human amnesic cases indicate that memory loss is associated with certain regions of the brain. The hippocampus and medial temporal lobes have received particular attention due to the profound amnesic deficits experienced by the patient H.M. In 1953, the case of H.M., the man who had his temporal lobes removed to alleviate his severe epileptic seizures, provided the initial breakthrough for memory research because H.M suffered severe memory impairments as a consequence of the surgery (Eichenbaum & Cohen, 2001; Corkin, 2002). The substantial number of opportunities to study the memory impairments of H.M. over the following five decades has continued to strengthen scientific knowledge and understanding about how particular brain regions are involved in memory processing.

The particular damage that H.M. sustained, which has since been more fully documented using MRI scans (Corkin et al, 1997) was bilateral, roughly symmetrical and included the medial temporal polar cortex, the amygdaloid complex, all of the entorhinal cortex, and just over half of the hippocampal formation (dentate gyrus, hippocampus, and subicular complex). Portions of the ventral perirhinal cortex and the entire parahippocampal cortex were largely intact. Outside the temporal lobes, the cerebellum demonstrated marked atrophy, and the mammillary nuclei were shrunken but the mediodorsal thalamic nuclei showed no obvious radiological changes. Accounting for age changes, the lateral temporal, frontal, parietal, and occipital lobe cortices appeared normal (Corkin et al, 1997).

Presumably as a consequence of this brain damage, H.M. has shown that he is severely impaired at acquiring and retaining new knowledge (anterograde amnesia). This impairment is global, that is, he is impaired whether the stories are verbal paired associates, supraspan digit strings, new vocabulary words, drawings, nonverbal paired associates, block diagrams, songs, common objects, or object locations (Eichenbaum & Cohen, 2001). His recognition memory impairments are also profound, whereby his performance on every type of recognition memory test is at chance. He is also unable to learn simple mazes and fails at delayed recognition of words, nonsense syllables, numbers, geometric drawings, faces, and tonal sequences (Squire, 1987). H.M. is also impaired at recalling events that happened some years prior to the onset of his amnesia (retrograde amnesia). Although H.M. has both anterograde and retrograde amnesia, the former is more severe and his more remote memory is relatively intact. For example, H.M. can remember his childhood and some general knowledge acquired earlier in his life (Corkin, 1984).

Despite H.M.'s capacity for learning and memory recall being severely impaired, he continued to maintain normal perceptual, motor and intellectual capacities (Eichenbaum & Cohen, 2001). H.M. is also able to briefly retain information in immediate memory (also referred to as short-term memory), as long as he is not interrupted (Baddeley & Warrington, 1973; Corkin, 2002). It was concluded from H.M's memory impairments that the hippocampus and medial temporal lobes are involved in memory deficits but not higher-order perceptual, motor and cognitive functions. Moreover it appeared that these brain regions were involved in the formation of new long-term memories, but not for immediate memory, or for retrieval of remote memory (Eichenbaum & Cohen, 2001).

Further breakthroughs in understanding memory processes came about through

studying amnesic patients, including H.M., because these patients demonstrated some specific abilities to acquire new information and retain it over periods of time. That is, H.M. and other amnesic patients can demonstrate normal capabilities with tests of memory that are aided by initial priming sessions, and they could learn mirror drawing perceptual skills and retain this skill over several months, despite their inability to remember having learnt the skill (Corkin, 2002). It was concluded from these empirical findings that the amnesic patients' memory impairments were limited to specific domains of learning and memory capacity (Cohen & Squire, 1980; Eichenbaum & Cohen, 2001). These dissociations in learning abilities incited theories about distinct forms of memory, i.e. declarative versus procedural memory, and promoted the proposals that there exist multiple memory systems within the brain that operate in parallel circuits, each processing different aspects of the information.

In addition, more selective lesion damage in humans to sub-component regions in the hippocampus and medial temporal lobes has resulted in a greater understanding of the neural basis to memory associated with these regions. For example, Scoville and Milner (1957, 2000) continued surgeries to resection the medial temporal lobes in further patients, although with less extensive damage than with H.M.. In a series of patients with damage to amygdala, uncus and most anterior portions of the hippocampus, these cases had less severe amnesia deficits than H.M.. While a patient with damage to only the amygdala and the uncus did not develop amnesia at all.

More recent clinical and neuropathological evidence of selective damage in the hippocampus reports the significant involvement of this region to memory processing. Rempel-Clower et al (1996) have reported three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation, which has been reported as a global memory deficit, with both material- and modality-general impairments. In addition Rempel-Clower and colleagues noted that extensive, temporally graded retrograde amnesia can occur after damage limited to the hippocampal formation. Other studies of unilateral damage to either the left or right hippocampus produces more material-specific memory impairments to either verbal or non-verbal components of memory processing, respectively (Eichenbaum & Cohen 2001). Thus there is a laterality to memory processing in the human hippocampus, as has been reported in the medial diencephalon (see Chapter 4 for details).

In addition to the hippocampus, the cortical regions of the medial temporal lobes are also implicated in memory processing. Briefly, the perirhinal and entorhinal cortical areas are also strongly implicated in memory processing associated with H.M.'s

impairments and those in other amnesic patients. Lesions resulting in damage in the medial temporal cortex areas also result in problems with new learning and in some cases temporally graded retrograde amnesia, yet they also do not appear to cause perceptual, motor, motivational or cognitive dysfunctions (Squire & Zola-Morgan, 1991; Zola-Morgan et al, 1989, 1994).

Animal lesions studies have also made selective lesions to the hippocampus and the medial temporal lobes and have reported similar evidence. For example, disruption to the hippocampus by lesions or damage to the fornix in rats produces impairments in spatial memory processing in radial mazes (O'Keefe & Nadel, 1978; O'Keefe et al, 1995; McDonald & White, 1993) and water mazes (Morris et al, 1982) and spatial reversal learning in Y- or T-mazes (O'Keefe & Nadel, 1978; Olton, 1979; Olton & Papas, 1979). In monkeys, disruption to the hippocampus causes impairments in delayed matching- and non-matching-to-sample tasks and scene (episodic-like) memory processing (Gaffan, 1992, 1994; Zola-Morgan et al, 1992). Other memory impairments occur in rats following hippocampal lesions, for example they show impaired learning of a conditioned fear response to the background context (contextual fear conditioning) but are unimpaired at learning the conditioned fear to a specific cue (cued fear conditioning; Phillips and LeDoux, 1992). Furthermore it is now proposed that processing of recognition memory in particular is associated with the adjacent perirhinal, parahippocampal and entorhinal cortex in both monkeys (Murray & Mishkin, 1986; Suzuki et al, 1993; Zola-Morgan & Squire, 1983) and rats (Mumby & Pinel, 1994; Young et al, 1996; Zhu et al, 1995).

All of this evidence suggests that memory may be dissociated from other forms of intellectual functions and that damage to the hippocampus, medial temporal lobes and medial diencephalon (as will be discussed in Chapter 4 in detail) impairs memory processing in many different aspects of material- and modality-specific domains. In addition, the types of memory processing associated with these regions is quite specific, with damage to the hippocampal formation disrupting only certain forms of memory, while leaving other forms intact. These observations have led to many specific theories about how memory processing is carried out in the brain.

3.2 Theories of Memory

There are many theories of how the brain functions in encoding and retrieval of information that it processes and learnt. This review introduces the current main theory

of memory processing, that is, the declarative / non-declarative model, initially proposed by Cohen and Squire (1980, cited in Eichenbaum & Cohen, 2001). This theory of memory has been since been adapted (Squire, 1991, 1992) and extended and elaborated by Cohen and Eichenbaum (1993; Eichenbaum & Cohen, 2001). Parallel multiple memory systems are also discussed (White & McDonald, 2002) and an alternative to this, the Multiple Attribute Model of Memory (Kesner, 1998). The Multiple Attribute Model has guided some of the current thesis' research on medial thalamic involvement in memory.

3.2.1 Declarative / Non-declarative (Procedural) Memory Model

Amnesic patients with damage to the hippocampus and medial temporal lobes have demonstrated in memory assessments that their impairments are specific to certain learning and memory capabilities; these findings have lead to theories about how the brain is involved in memory processes. It has been proposed that there are two independent components to memory. One of these components is declarative while the other is non-declarative.

The declarative component involves memory for the recall of facts and events, which in humans is brought into conscious recollection and can be expressed explicitly in a variety of ways, most prominently by verbal reflection on a learned fact or past experience (Cohen & Squire, 1980; Cohen, 1984; Squire, 1987, 1992). Neuropathological studies and clinical evidence of amnesic patients suggests the integrity of the medial temporal lobes and medial diencephalon are critical for normal declarative memory processing capabilities (Eichenbaum et al, 1994; Squire, 1992). Declarative memory is also further subdivided into episodic and semantic memory components (Tulving, 1972, cited in Eichenbaum, 2001). Episodic memory refers to the capacity to remember specific personal experiences that occur in unique spatial and temporal context. Conversely, semantic memory refers to the capacity to acquire world knowledge that is in relation to facts about the content and meaning of new language, social structure, geography, and many other forms of general knowledge (Tulving, 1972, 1993, cited in Eichenbaum & Cohen 2001). According to Tulving, normal episodic memory processing is dependent on an intact hippocampus, while semantic memory is processed by other structures in the brain. Furthermore these two components of declarative memory can be dissociated in some amnesic patients, whereby they may have intact semantic memory and be deficient in processing of

episodic (personal) forms of memory (Parkin, 1987; Vargha-Khadem et al, 1997, 2003) or vice versa (Temple & Richardson, 2004).

The non-declarative or procedural component to memory describes memory for various motor, perceptual, and cognitive skills, which are generally believed to be unaffected by damage to the medial temporal lobes or medial diencephalon (Squire, 1992; Eichenbaum & Cohen, 2001). In humans, the processing of memory by the non-declarative component is presumed to be conducted without conscious recollection. Non-declarative memory involves memory for skills, habits, priming, simple classic conditioning and non-associative learning, that is, prior experience affords abilities in the future without conscious access to the past events (Squire, 1992). Non-declarative memory involves many different regions of the brain (Squire, 1994; Squire & Knowlton, 2000). For example, a common perspective is that the striatum is involved in processing skills and habit learning (egocentric response information), while the cerebellum processes simple classical conditioning of skeletal musculature, the amygdala is involved in processing emotional responses, and priming is regulated by the posterior neocortex (Squire, 1992; also see Fig. 4 on p.23 for a schematic illustration of the declarative / non-declarative model of memory processing).

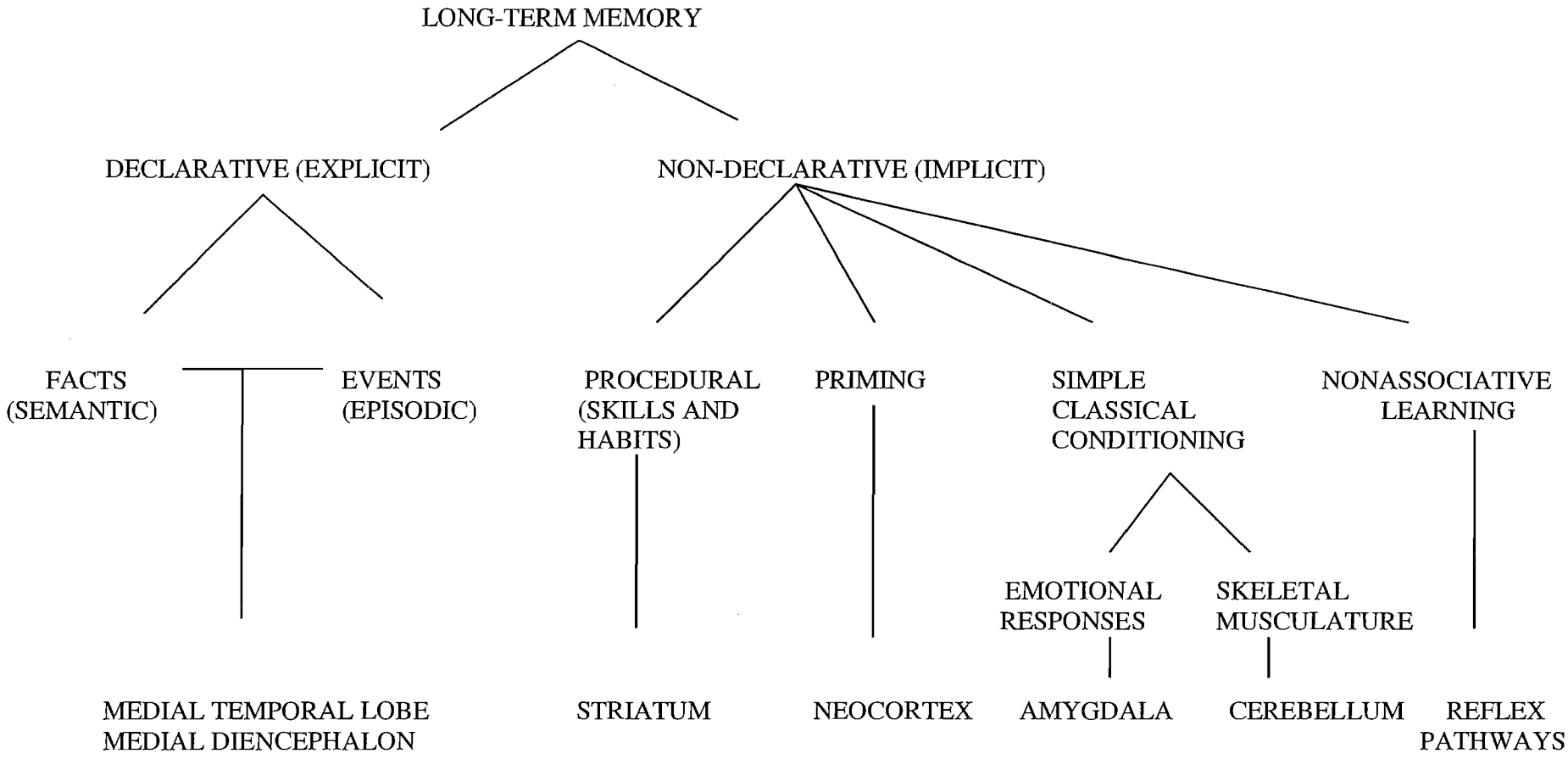

Fig. 4. A Taxonomy of Mammalian Memory Systems.
This taxonomy lists the brain structures and connections thought to be especially important for each kind of declarative and non-declarative memory. Adapted from Squire, 1992.

The notion of declarative / non-declarative memory in animals has also been adapted to animal models of learning. Olton (1983) devised a related dichotomous model to explain memory processing in relation to animals learning a new task, especially rats. According to Olton, within learning any new task there are two types of memories that organise the critical information into two different systems, namely working and reference memory. The working memory system is hippocampal-dependent and is defined as memory for the specific, personal and temporal context of a situation. According to Kesner (1998), this working memory definition translates into 'memory for events that occur on a specific trial in a task, biasing mnemonic coding toward the processing of incoming data'. In contrast, Olton proposed the reference memory system is non-hippocampal dependent and is defined as memory for rules and procedures (general knowledge) of a specific situation. This reference memory definition translates into 'memory for events that happen on all trials in a task, biasing mnemonic coding toward the processing of expectancies based on the organisation of the extant memory' (Kesner, 1998).

3.2.2 An Elaboration to the Declarative / Non-declarative Model of Memory

Eichenbaum and Cohen (2001) proposed an elaboration of the declarative / non-declarative model of memory by suggesting that the dual process distinction 'also posits fundamental differences in the nature of memory representations that underlie performance'. Eichenbaum and Cohen argue that declarative representations permit the processing and storage of comparisons among learning events and among the items within learning events. Additionally, the critical property of declarative memory that the hippocampal-dependent system supports is a relational representation of items in memory. That is, 'the nature of the declarative representation is fundamentally relational and can be envisioned as a multi-dimensional network of memories entailing a highly interconnected network with connections among information elements characterising possible relations'. Furthermore and as a consequence of the relational nature of declarative representations, another defining property of declarative memory is its representational flexibility, whereby stored representations are broadly accessible, used flexibly to guide performance under an enormous range of testing conditions and furthermore they can be expressed independently of the circumstances in which the information was initially acquired.

In contrast, Eichenbaum and Cohen (2001) propose that the non-hippocampal dependent system (i.e. non-declarative or 'procedural' memory) is based on the representation of a single stimulus or a single configuration of stimuli. These non-declarative memories are 'isolated in that they are encoded only within the brain modules in which perceptual and motor processing is engaged during learning'. Therefore these memories are inflexible and can not be retrieved in novel situations. That is to say, other brain regions (not including the hippocampus) mediate simpler forms of learning and memory (Eichenbaum & Cohen, 2001).

Accordingly these revisions to the declarative / non-declarative account of memory processing are proposed to explain with greater coherence the underlying mechanisms of hippocampal-dependent and non-hippocampal-dependent involvement in learning and memory capabilities for both humans and animals than is the case with other memory models, e.g. Squire (1992), Schacter (1987) and Eichenbaum and Cohen (2001).

The most established models of memory briefly described above can be characterized as dual memory system models, whereby one component of the dual model emphasizes the importance of the hippocampus and medial temporal lobes for all forms of declarative or working memory processing, as well as all relationships of information processing (Eichenbaum & Cohen, 2001), while the other component (non-declarative / procedural / reference memory) represents a composite of other brain structures. These dual process theories of memory have led onto further proposals about distinct types of memory processing being mediated by distinct functional systems in the brain. One of these theories, namely the Parallel Multiple Memory Systems theory of White and McDonald (2002) is discussed briefly below.

In a particularly convincing experimental design that engaged different memory systems associated with different structures of the brain, McDonald and White (1993) were able to demonstrate that following lesions to these specific structures, triple dissociations in memory processing can occur. Moreover the experimental stimulus, rewards and approach responses for the rats were the same across all three tasks. The triple dissociation reported was that the amygdala is involved in stimulus-reward associations, the hippocampus is involved in stimulus-stimulus associations and the dorsal striatum is involved in stimulus-response associations (McDonald & White, 1993). A multiple parallel memory systems theory has been proposed (White & McDonald, 2002), whereby each system consists of a

series of interconnected neural structures, with the 'central structures' of the three systems being the hippocampus, dorsal striatum and amygdala. Information that is processed and stored about events for the individual flows through each of these systems independently, with each system specialized to represent a different kind of relationship among the elements (stimulus events, responses, and reinforcers, which correspond to the respective systems mentioned above). While it is proposed that the systems work independently with respect to both memory and other cognitive functioning, they may also interact both cooperatively (to produce similar behaviour) or in competition (to produce different behaviours).

In the next section, an alternative theory of multiple memory systems processing that has been proposed by Kesner (1998) is discussed, namely the Multiple Attribute Memory Model. This model is presented as it provides useful behavioural tasks that may be helpful in analysing thalamic function in memory.

3.2.3 Multiple Attribute Memory Model (Kesner, 1998)

An alternative theory to that of the typical declarative / non-declarative stance is a multidimensional model of memory. Kesner and DiMattia (1987) originally proposed a neurobiology of a dual-process model centred around the different structures of the entire brain. More recently, Kesner (1998) suggests that memory is a great deal more complex and involves many neural systems (in conscious memory processing, a.k.a. declarative memory) in addition to the hippocampus. This dual-system model assumes that any specific memory is organised into a data-based memory system (akin to episodic or working memory) and a knowledge-based memory system (akin to semantic or reference memory).

The data-based memory system subserves temporary representations of incoming facts and events that are currently occurring within specific external and internal contexts and are usually subjective in nature. The emphasis for this data-based memory system is on bottom-up processing and it is crucial during initial learning; it continues to be of importance even after initial learning in situations where unique or novel trial information needs to be remembered.

The other memory system of the attribute model of memory, the knowledge-based system, subserves more permanent representations of previously stored information in long-term memory (i.e. one's general knowledge of the world). This system can operate in the abstract in the absence of incoming data. As Kesner (1998) has proposed, the emphasis of the knowledge-based system is on top-down processing; the system is more crucial after a task has been learned, given that the situation is invariant and familiar. Additional to these two systems is a rule-based memory component, which involves different regions of prefrontal cortex (PFC) governing the most important attributes in memory processing.

The most important attributes identified in the multiple attribute model of memory for both humans and animals are space, time, response, sensory perception, affect and, specific to humans, language. Each of these attributes is functionally separate but interdependent. The attributes are further organised into the data-based and knowledge-based memory systems and it is proposed that within the two systems different neural structures are involved in processing information related to these specific attributes. These different neural structures of the data-based and knowledge-based systems do not work alone, but rather they operate in conjunction with other structures interconnected by neural pathways, which are processing information previously stored in memory thus forming the neural circuits for the event-based and knowledge-based systems. Furthermore, these substrates can operate independently of each other as evidenced by the existence of double dissociations following relatively localised brain injury in both humans and animal lesion models. Fig. 5 depicts detailed information about the neural structures involved in each of the data-based and knowledge-based (and rule-based associated) memory systems and how they are each linked to specific memory attribute processing circuits (see Fig. 5 on p. 28).

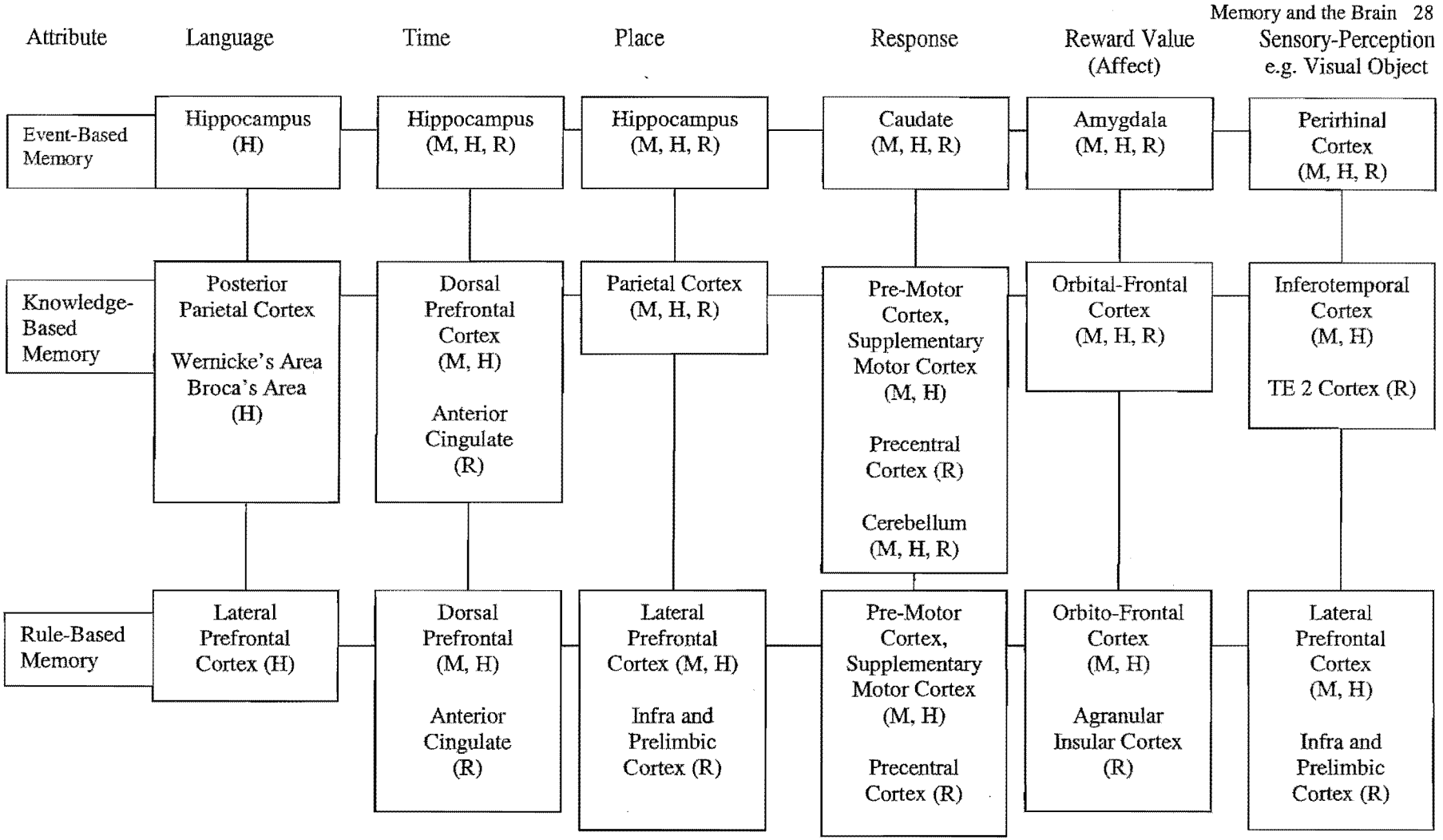

Fig. 5. The Multiple Attribute Model of Memory. Adapted from Kesner (1998).

Kesner's attribute memory model encompasses a number of brain structures (and their interconnected pathways) involved in memory processing but it does not include the medial thalamus. Furthermore the role of the medial thalamus and diencephalon in any of the above-mentioned theories of memory has thus far been mentioned but not fully detailed (Zola-Morgan & Squire, 1993; Squire et al, 1993). Aggleton and colleagues (Aggleton & Brown, 1999; Aggleton & Sahgal, 1993) have investigated, in particular, the role of the anterior thalamic nuclei of the medial diencephalon (as will be discussed in detail in the next chapter), but very little is resolved about this regions, or many other medial thalamic regions, involvement in memory processing, despite the severity of memory impairments following brain injury to the medial thalamus. Furthermore the medial thalamus has significant links with many of these structures that Kesner (1998) proposes are involved in processing information related to the multiple attributes of memory. For example, the anterior thalamic nuclei are strongly interconnected with the hippocampal system as briefly detailed in Chapter 2 and to be fully discussed in Chapter 6. Therefore, although the attribute model seems to provide a contemporary theory to memory processing, it is proposed in the current dissertation that The Attribute Memory Model, along with those models of memory proposed by White and McDonald (2002), Squire (1992), and Cohen and Eichenbaum (2001) must be adapted to incorporate within their frameworks the contributions of the medial thalamic nuclei to memory processing.

In summary then, current theories about memory processing in the brain are all in accord that the hippocampus plays a critical role, albeit in certain types of memory processing. Controversy remains regarding the exact functions of the hippocampus in memory processing, but this is beyond the scope of this thesis. Needless to say there are, however, other researchers who argue against the notion of multiple memory systems (Gaffan, 2002; Easton & Parker, 2003), so for the sake of theoretical balance these objections are noted briefly.

Gaffan and colleagues (Gaffan, 2002; Gaffan et al, 2002; Easton & Parker, 2003) propose that due to the plasticity of the cortex, memory traces are stored in many cortical areas rather than in a specialised memory system that is restricted to the medial temporal lobe. Gaffan and colleagues argue against the proposal of multiple memory systems operating in the brain as this notion 'infers that the structures of the medial temporal lobes are specialised for the acquisition and storage of memories'. Furthermore these authors propose that the prefrontal cortex has an

important role in learning and memory processes, but that this role is not specialised to one particular form of memory or type of functioning (Gaffan, 2002).

Moreover, Gaffan and colleagues (Gaffan et al, 2001) suggest that sub-cortical disconnection of the temporal cortex offers the best explanation for the dense amnesia after medial temporal lobe lesions, in both humans and non-human primates. Briefly, Gaffan and colleagues propose that dense amnesia suffered following medial temporal lobe injury is not due to the removal of specific cortical areas because one area is not in itself that specialized to process and store memories, (i.e. functions of the temporal cortical areas are not just in memory, but also in perception and motor control), but rather to the widespread disruption of temporal cortical function that is produced by disconnection of the temporal cortex from basal forebrain and midbrain neuromodulatory (mainly cholinergic) factors. Following several experiments in monkeys that have disconnected fibre pathways running between the sub-cortical structures and medial temporal lobes, Gaffan and colleagues have concluded that dense amnesia is produced with disruption to all three routes of axon transportation, namely via the fornix-fimbria, via the fibres of passage through the amygdala, and via the anterior temporal stem (the white matter surrounding the amygdala dorsally and laterally; Selden et al, 1998), while less severe memory impairments are observed with disruption to only one or two pathways. As proposed by Gaffan (2002), a memory system must receive and store complex information, but the ascending axons from the basal forebrain and midbrain only convey an arousal signal rather than complex information (Gaffan & Easton, 2000; Gaffan, 2002). Thus ultimately memories are processed and stored in widespread cortical areas.

Furthermore, Easton & Parker (2003) propose that this cholinergic explanation for dense amnesia in humans provides, not only an explanation for the symptoms of patients with medial temporal lobe damage, but also those with mammillary bodies lesions, medial thalamic damage and direct damage within the basal forebrain. As indicated in Easton and Parker's model for primate learning, their proposals stem from the notion that there is a route of communication between the frontal cortex and inferior temporal cortex and hippocampus via the basal forebrain, which is critical to memory encoding; interruption to this circuit at any stage will result in severe and global anterograde amnesia. As noted by Easton and Parker (2003) evidence in humans and monkeys (Aggleton et al, 2000; Gaffan, 1994; Parker & Gaffan, 1997a, b) is consistent with this proposal as damage to the Delay and Brion circuit (1969; cited in Aggleton & Brown, 1999) produces similar levels of impairment in scene memory, whether

the lesions are in the fornix, mammillary bodies, or the anterior thalamus, but apparently not with removal of the cingulate cortex. Furthermore, similar evidence of related deficits has also been reported in rats using spatial memory tasks, considered analogous to episodic-like declarative memory in humans (Aggleton & Pearce, 2001), following lesions to structures in the Delay and Brion circuit (Aggleton & Brown, 1999).

The following chapter indicates in detail some examples of clinical cases of thalamic amnesia. The types of memory deficits are discussed in comparison to the clinical cases of the medial temporal lobes amnesia and finally the theories associated with medial thalamic involvement in memory processes are discussed.

Chapter 4

Medial Diencephalic Involvement in Human Amnesia

This chapter presents clinical evidence implicating the medial diencephalon in learning and memory processes with the main focus on the medial thalamus, especially the anterior (AT), intralaminar (ILn) and mediodorsal (MDn) nuclei. This is followed by a review of the proposed theories about how the medial thalamic nuclei contribute to human amnesia.

4.1 Introduction

It is widely recognised that the episodic memory processes that are disrupted in anterograde amnesia are represented by interactions between the medial temporal lobes and the medial diencephalon, yet the neural basis of the medial thalamic nuclei involved continues to be debated in the literature (Aggleton & Brown, 1999; Easton & Parker, 2003; Gaffan, 2002; Mair et al, 1999; Markowitsch, 1999; Van der Werf et al, 2000, 2003a, b). The medial thalamic structures most frequently identified as being critical for the memory deficits are anterior (AT), mediodorsal (MDn), and the intralaminar (ILn) / midline nuclei. White matter fibre tracts, particularly the internal medullary lamina (IML) and mammillothalamic tract (MMT) are also strongly implicated in human cases (Burk & Mair, 1998; Calabrese et al, 1993; Graff-Radford et al, 1990; Mair, 1994; Markowitsch, 1988; Van der Werf et al, 2000, 2003).

The study of thalamic amnesia encounters difficulties because of the small size and close proximity of nuclei and fibre tracts in the areas of the medial thalamus that are thought to be critical for remembering (Markowitsch, 1988). Furthermore, it is extremely rare that patients will have selective bilateral damage in the medial thalamic nuclei (Markowitsch, 1982; 1988; 1999). In addition, even new imaging technology used with intact individuals is not yet

advanced enough to highlight specific and detailed enough activity in each of these individual sub-cortical nuclei.

4.2 Clinical Evidence of Diencephalic Amnesia – Human Neuropsychology

Based on assessments of the alcoholic Korsakoff syndrome (KS), cognitive neuroscientists have known for some time that damage to the medial diencephalon causes amnesia in humans (Victor et al, 1971). It is also widely known that damage to the medial thalamus in particular causes amnesic deficits, which can occur following cysts, tumours, infarcts, haemorrhage or vascular accidents. A review of each of these brain disorders related to the medial thalamus follows, which focuses initially on KS.

4.2.1 Korsakoff Syndrome

Korsakoff syndrome (KS) has been defined as a disproportionate impairment of memory relative to other aspects of cognitive function, resulting from alcohol abuse and / or thiamine deficiency (Kopelman, 1995). The first formal descriptions of a link between alcohol abuse and profound amnesia were by Lawson (1878; cited in Kopelman, 1995) and Korsakoff (1887; 1889, cited in Kopelman, 1995). An acute Wernicke's encephalopathy, which was first described in 1881, usually precedes the KS or psychosis, but in some cases it is insidious. The encephalopathy can be effectively treated sometimes with thiamine replacement if intercepted early enough; otherwise, it can proceed on to KS. Korsakoff syndrome patients have memory deficits that can encompass both retrograde and anterograde components, with varying degrees of impaired executive functioning. Wernicke's encephalopathy can be brought on by various aetiologies but KS is virtually always the result of prolonged alcohol abuse (Kopelman, 1995). The disorder may be clinically diagnosed alcoholic KS according to the ICD-10 and DSM-IV criteria (for alcohol-induced amnesic syndrome or alcohol-induced persisting amnesic disorder). It is important to note though that KS patients have brain damage beyond the medial diencephalon and that severe amnesia is not the only significant clinical manifestation of the syndrome.

Both structural and metabolic studies of KS patients have produced variable findings about the neural basis for the memory impairments, causing debate over the critical lesion sites

(Kril & Halliday, 1999; Mair, Warrington & Weiskrantz, 1979; Mayes et al, 1988; Victor et al, 1989; Visser et al, 1999). Discrepancies have resulted, in part, from the limited resolution of different techniques used, poorly defined structural boundaries for individual nuclei using magnetic resonance imaging (MRI), and the analysis of only a limited range of cognitive measurements (Reed et al, 2003).

An influential neuropathological report of KS patients by Victor and colleagues (1971, 1989) suggested a neural basis for the amnesic syndrome. These researchers concluded that while atrophy of the mammillary bodies is a consistent feature of KS, the degeneration in the mediodorsal thalamic nuclei is a better predictor of the memory impairments (Victor et al, 1989). Subsequent investigations by other researchers have provided evidence that the nuclear size, and populations of neurons within the anterior thalamus and mammillary body are particularly susceptible to excessive alcohol consumption (Belzunegui, Insausti, Ibanez, & Gonzalo, 1995). More recently, functional changes in neuronal numbers of nuclei within the medial diencephalon in particular are proposed to be responsible for the amnesic deficits (Harding et al, 2000; Kopelman, 2000).

Needless to say, KS is brought about by chronic abuse of alcohol, and it is widely known that alcohol affects many regions of the brain. For example, the frontal cortical regions together with their associated cerebral white matter appear to be most sensitive to alcohol-induced damage (Kril & Halliday, 1999). Ventricular enlargement occurs in alcoholics but it has been demonstrated using CT scan that ventricular enlargement is reversible following a period of abstinence (Schroth et al, 1988; Zipursky et al, 1989, cited in Kril & Halliday, 1999). PET scan has revealed changes in specific cortical areas include the parietal and frontal lobes of alcoholics (Paller et al, 1997). Damage to the parietal lobes affects processing of long-term memory and damage to the frontal lobes affects higher order cognitive functions like planning, coordination and utilising strategies in behavioural tasks (Eichenbaum & Cohen, 2001; Kesner, 1998; Fuster, 2001).

Researchers have reported evidence of frontal lobe dysfunction associated with chronic alcoholism. For example, Adams and colleagues (Adams et al, 1995) have reported correlational relationships between neuropsychological deficits in several higher order 'executive' functions, like planning, abstract reasoning, and working memory, and impaired FDG-metabolism in the frontal lobes of alcoholics. Additionally, Paller and colleagues (1997) reported both frontal and parietal cortical hypometabolism in reformed alcoholics with KS

psychosis, which suggests that cortical dysfunction contributes to the amnesic symptoms associated with KS, but they did not compare their findings with levels of cortical brain atrophy in non-amnesic alcoholics. Recently an intriguing study demonstrated increased levels of activity in the left dorsolateral prefrontal cortex and the anterior thalamus of alcoholics, as recorded by functional MRI, after a sip of alcohol given while viewing alcohol-specific cues (George, Anton, Bloomer et al, 2001).

Sub-cortical areas affected by chronic alcohol consumption include the medial diencephalon, the pons, medulla, cerebellum and hypothalamus (Harper et al, 2003). In order to determine the neural substrate responsible for the memory deficits observed in alcoholic Korsakoff syndrome, Harding and colleagues (Harding et al, 2000) have conducted detailed neuropathological analyses of the diencephalic regions suggested to be involved in episodic aspects of declarative memory processing. Specifically, Harding and colleagues compared the mammillary bodies, MDn and AT thalamic nuclei in non-alcoholic controls, alcoholic controls, non-amnesic alcoholics with Wernicke's encephalopathy and amnesic alcoholics with Korsakoff syndrome. They reported that there was neuropathology in the medial diencephalon in all alcoholics with Wernicke's encephalopathy: the neuronal numbers in the mammillary bodies and MDn were substantially reduced compared to those of controls (53% and 52% respectively) and the neuronal numbers in the AT were reduced to 86% of controls. By contrast, the neuronal numbers in these medial diencephalic structures were significantly more reduced in amnesic alcoholics with Korsakoff syndrome: neuronal numbers for the mammillary bodies were reduced to 32%, for the MDn reduced to 36%, and in particular for the AT the reduction was to 47% compared to non-amnesic alcoholics with Wernicke's encephalopathy, alcoholic controls and controls. Therefore although neuronal loss to the mammillary bodies and MDn was significantly reduced in the Wernicke's encephalopathy patients, the amnesic Korsakoff syndrome was not inevitable. Instead increased neurodegeneration of the AT was the only consistent atrophy found in the amnesic alcoholics suffering Korsakoff syndrome, which was suggested as critical for their amnesia (Harding et al, 2000).

Harding, Halliday and colleagues have undertaken similar neuropathological studies of the cerebral cortex (Kril et al, 1997) and the hippocampus (Harding et al, 1997). Kril and colleagues observed significant neuronal degeneration and volumetric reductions within the cortical regions, but they noted that the degree of degeneration was similar in alcoholics both

with, and without KS. Furthermore the study that assessed hippocampal atrophy in association with chronic alcoholism (Harding et al, 1997) found no neuronal loss in the sub-regions of the hippocampal formation, although a significant reduction in volume was reported. This significant volumetric loss of the hippocampal formation was attributed to the reduced white matter in alcoholics who were not abstinent at time of death (Harding et al, 1997). In conclusion, Harding and colleagues have stated that while many brain regions are affected by the chronic alcohol abuse, the neurodegeneration of the AT is the only differentiating lesion in those alcoholic cases with the amnesic Korsakoff syndrome (Harding et al, 2000).

Therefore, from the above evidence presented it appears that damage in KS patients is sustained in a variety of brain regions, however medial thalamic damage, in particular, atrophy of the AT, is critical to producing the amnesic syndrome. The damage in other regions may contribute to or compound the amnesic deficits (e.g. damage to the frontal and parietal lobes) and produce individual variability (e.g. damage to the mammillary bodies) that is correlated with the duration of exposure to excessive amounts of alcohol (Harding et al, 2000).

4.2.2 The Amnesic Syndrome in KS

The KS has been described as multi-faceted amnesic syndrome due to the significant amount of brain damage that causes a variety of memory deficits (Grossman & Butters, 1986). Many studies have investigated the differences in memory impairments between amnesics diagnosed with KS and amnesics with medial temporal lobe (MTL) damage. Many similarities and differences have been reported and a brief review follows.

KS patients and MTL amnesics are suggested to show similar impairments in tests of recognition and recall. Kopelman and Stanhope (1998) investigated a group of amnesics with damage sustained in the diencephalon (13 x KS patients and 2 x patients suffering amnesic syndromes following surgery and irradiation of a Pituitary adenoma: MRI showed damage in the AT, mammillary bodies, mammillothalamic tract and fornix) and a group of amnesics with damage sustained in the MTL (9 x herpes encephalitis patients and 4 x hypoxic patients and 1 x a long-time epileptic with CT scans showing temporal lobe atrophy). They reported no differences between the two groups of amnesics using tests of recall and recognition memory when exposures times were varied across patient groups in order to match group mean recognition memory scores as closely as possible. Kopelman and Stanhope noted that the 4

hypoxic patients in the MTL amnesic group also demonstrated thalamic hypometabolism on PET scan, although when these patients were excluded from the MTL amnesic group the findings of memory impairments remained similar. Patients with focal frontal damage were also assessed in the study and their recall and recognition memory impairments were not as substantial as either the KS or MTL amnesics (Kopelman & Stanhope, 1998).

With tests of executive functioning, differences have been demonstrated between amnesic KS patients and MTL amnesics. Prefrontal damage often results in perseveration on the Wisconsin card-sorting test (WCST). Such patients will characteristically perseverate a discovered sorting rule, maintaining performance consistent with an old rule long after normal subjects have discovered the new rule. H.M. (our classic MTL amnesic) performs card-sort tasks as well as normal subjects (Eichenbaum & Cohen, 2001), whereas KS patients often have deficits in WCST for both category scores and perseveration errors (Downes et al, 2002; Kopelman et al, 1999; Reed et al, 2003). On the other hand, KS patients can show variable impairments on FAS and the Cognitive Estimates Test, which are both tests of other forms of frontal executive dysfunction (Downes, et al, 2002; Reed et al, 2003; Brand et al, 2003). KS patients are also impaired in temporal order memory processing (Downes et al, 2002; Graff-Radford et al, 1990; Shuren et al, 1997), generally also associated with frontal lobe impairments (Fuster, 1991; Milner et al, 1985). MTL amnesics also demonstrate deficits in temporal order processing when matched for other abilities with controls (Downes et al, 2002).

Amnesics with MTL damage, KS patients and controls have been assessed on spatial memory tests using three different conditions: short delays (0 – 8s), allocentric and egocentric conditions (Holdstock, Mayes, Cezayiril, et al, 1999). As Holdstock and colleagues indicate when making use of allocentric spatial memory processing, a participant utilises an array of external stimuli or landmarks to navigate successfully in the environment, while during egocentric spatial memory processing the observer navigates locations relative to their own body position (O'Keefe & Nadel, 1978; Holdstock et al, 1999). Both the MTL amnesics were unimpaired at the short delay condition, but they demonstrated deficits in the allocentric spatial processing condition with longer delays. In the egocentric condition one of the MTL amnesics was impaired at the longer delays whereas the other was unimpaired in this condition. The KS patients were significantly impaired at all short delays, and were similarly impaired at both allocentric and egocentric information processing conditions compared to controls. Holdstock and colleagues propose that the allocentric deficits are due to dysfunction in the Papez circuit

(1937), highlighting the involvement of hippocampus and additional structures within the circuit being critical in spatial memory processing. In contrast, the authors proposed that the egocentric deficits may be due to impairments following injury in parietal or frontal cortex of KS patients (Paller et al, 1997); both these regions have been implicated in egocentric spatial processing (Fuster, 1980; McDaniel et al, 1995). On the other hand it was also suggested that the egocentric information processing deficits may be due to diencephalic structural damage. This proposal was attributed to differences in brain damage shown on MRI scans of the two MTL amnesics. In the MTL amnesic who showed deficits in egocentric spatial memory, there was evidence of enlarged lateral and third ventricle spaces, which may indicate atrophy of diencephalic structures such as the thalamus. Furthermore there was no evidence of extensive damage to parietal or frontal cortex in either MTL amnesic (Holdstock et al, 1999).

KS patients also exhibit difficulties in affective processing. These impairments include, for example, difficulties with interpreting the meaning of affective prosody in the absence of semantic cues as to the emotional content of sentences (Snitz et al, 2002), and difficulties in an affective judgment task comprising negative, neutral, and positive words (Brand et al, 2003). The deficits in affective processing of KS patients have previously been attributed to injury of particular diencephalic and sub-cortical brain structures thought to process emotional expression (Grossman & Butters, 1986) or related to the damage sustained in the prefrontal cortex (Brand et al, 2003). Recently, Snitz et al (2002) speculated the involvement of the basolateral circuit (connecting limbic, anterior temporal and prefrontal structures) in processing of affective prosody, which is impaired in KS patients.

4.3 Other Clinical Evidence of Thalamic Amnesia

As indicated in the above review of KS, brain damage to the medial thalamus in particular the AT is implicated in amnesic deficits. Now we turn to other clinical evidence that implicates the medial thalamic nuclei in amnesic deficits. Further clinical evidence is reported of infarcts to the medial thalamus, prion diseases, and other neuropsychological disorders. Before reviewing this evidence it is important to highlight some caveats to the interpretations of the clinical literature.

Discrepancies in memory and behavioural impairments following brain injury in the medial diencephalon may be the result of differences in how the two halves of the human brain

process data. In its lateral asymmetry, thalamic organisation parallels cortical organisation in that the left thalamic structures are implicated in verbal activity and right thalamic structure in nonverbal aspects of cognitive performance (Lezak, 1995). For example, left thalamic lesion patients have not lost the ability to communicate verbally but they may demonstrate decreased verbal fluency and spontaneity of speech, verbal memory and learning disorders and lower scores on verbal tests. Right thalamic lesion patients can have visuospatial deficits, for example difficulties with face or pattern recognition and pattern matching, maze tracing, and with design reconstruction. A further thought to keep in mind is that some of the studies mentioned have reported findings using relatively small sample sizes and moreover they include thalamic injury that may involve a high degree of overlap into adjacent target areas of interest.

4.3.1 Strokes and Infarcts in the Medial Thalamus

In contrast to KS, the impact of localised vascular lesion(s) to the brain result in an acute onset, although much like the medial thalamic damage sustained in KS, infarcts in the medial thalamus are not limited to one nucleus or a separate grouping of nuclei. Therefore the clinical literature regarding infarcts in the medial thalamus is also not clearly conclusive about the neural basis for diencephalic amnesia (Macchi, 1997; Schmahmann, 2003; Van der Werf et al, 2000, 2003).

The vascular supply to the thalamus is well documented, despite many researchers referring to each arterial supply with different nomenclature. There appear to be four principal sources, which can aid, to some degree, with the grouping of infarct patients to determine commonalities of deficits. One further complication is the variability in blood supply to the thalamus across individuals (Schmahmann, 2003). The four principal sources are: A) the tuberothalamic artery (also referred to as the inferior thalamic peduncle, thalamic polar artery or the premammillary peduncle) originates in the posterior communicating artery. The tuberothalamic artery provides vascular supply to the rostral anteroventral-medial part of the thalamus, that is to the AT, rostral reticular nucleus, ventral anterior, ventral lateral and ventromedial nuclei, extending posteriorly to the mammillothalamic tract and partially to the rostrovental part of the MDn. B) The paramedian artery (also referred to as the thalamoperforate peduncle, or the retromammillary peduncle) originates in the basilar artery bifurcation. The paramedian artery provides vascular supply to the ventromedial part of the

thalamus including ventral mediodorsal, anterior intralaminar, parafascicular, centromedian nuclei, and the inferomedial part of the laterodorsal and the lateral posterior nuclei. This artery can sometimes replace the polar artery territory supply too, which may be absent in some individuals. C) The inferolateral peduncle (also called the thalamo-geniculate peduncle) originates from the posterior cerebral artery. This artery gives vascular supply to the lateral thalamus, including the ventral posterior nucleus and the inferolateral part of the pulvinar. D) The choroidal artery (also referred to as the posterior choroidal arteries) originates in the postero-medial and postero-lateral branch from the posterior cerebral artery. This choroidal artery gives vascular supply to the posterior part of the lateral and medial geniculate bodies, to the dorsal part of the anterior thalamic nuclei (anteroventral, anteromedial and anterodorsal nuclei), to the dorsolateral group (lateroposterior, laterodorsal, pulvinar), to the dorsal part of the mediodorsal nucleus with collateral branches also to the posterior part of the centromedian and medial part of the ventral posterior medial nuclei (Macchi, 1997; Schmahmann, 2003). As is indicated from the above descriptions of the four main sources of vascular blood supply to the thalamus there is considerable overlap across many nuclei proposed to disrupt memory processes. Therefore the symptomatology related to infarctions may vary according to the occlusions to a single source and to the extent of the territory supplied. Haemorrhagic lesions will produce even more varied damage. Thus the interpretation of thalamic function based on pathophysiological correlations between symptomatology and thalamic damage based on vascular lesions, may differ from case to case, and is sometimes controversial (Macchi, 1997).

Despite these difficulties, there are many reports of behavioural studies involving patients with vascular damage to the medial thalamus. Many of the studies implicate the anterior regions of the medial thalamus, especially the AT as being responsible for the amnesic syndrome associated with damage in the medial thalamus (e.g. Ghika-Schmid & Bogousslavsky 2000; Van Cramon et al, 1985). There is also evidence for both MDn involvement, especially in relation to contextual memory impairments (e.g. Shuren et al, 1997; Zoppelt et al, 2002), and ILn involvement, especially in relation to dysexecutive functioning (Van der Werf et al, 1999). In addition, others have argued that the amnesic syndrome is caused by damage to the many fibres of passage that transverse the thalamus (e.g. Graff-Radford et al, 1990; Markowitsch, 1988; Van der Werf et al, 2000).

Ghika-Schmid & Bogousslavsky (2000) report on amnesic patients who suffered from their first acute stroke causing damage limited to the anterior part of the thalamus, due to

disruption of the tuberothalamic artery. MRI scans indicated that the infarcts were limited to damage in the anterior thalamic nuclei, as well as the mammillothalamic tract and anterior part of the internal medullary lamina. All patients demonstrated severe perseverative behaviour in thinking, spontaneous speech, and all memory and executive tasks. In addition, impairment of anterograde memory was a constant finding, with better performance for recognition. Patients also had aphasia, with word-finding difficulties and lack of speech initiation but unimpaired comprehension, repetition, and written language abilities. The authors reported no marked right verses left lateralization of language or memory function. The authors concluded that although memory impairment and transcortical aphasia are not specific for anterior thalamic infarction, the findings from their study showed that when these features are combined with palipsychism (superimposition of mental activities normally processed sequentially), perseverations, dysexecutive features and apathy, the clinical picture becomes highly suggestive of this type of lesion (Ghika-Schmid & Bogousslavsky, 2000).

In another report of ischemic lesions, Zoppelt and colleagues (Zoppelt, Koch, Schwarz and Daum, 2003) compared deficits in memory for recollection and familiarity following relatively selective lesions to MDn or ventrolateral thalamic nuclei (VL). Zoppelt and colleagues report the MDn contribute to recollection, with some evidence for medial MDn involvement in familiarity, while following lesions to the lateral MDn group only recollection was impaired and not familiarity, whereas damage in VL leads to memory and executive dysfunction. It is suggested that these impairments may be due to disruptions of thalamic structures connecting to the cortical areas. This familiarity reduction may be due to disconnection of the medial MDn with perirhinal cortex, a proposal also suggested by Aggleton and Brown (1999, see below). The medial MDn has connections with entorhinal, perirhinal and temporal polar cortices as well as the amygdala, and lesions to both entorhinal and perirhinal (Meunier et al, 1993), but not the amygdala (Murray & Mishkin, 1998), have shown deficits in monkeys on object recognition tasks.

Further conclusions noted by Zoppelt et al (2003) suggest that deficits reported with their lateral MDn patients are due to a disruption between the lateral MDn and dorsolateral PFC, supporting the notion of the lateral MDn being involved in contextual memory processing. Other researchers have drawn similar conclusions. For example, Shuren, et al (1997) reported deficits in temporal order memory processing following restricted lesions to the lateral MDn.

These authors suggested this region may process information related to context (when, where) rather than content (what) per se.

Other studies of infarcts in the thalamus have suggested that damage in the medial thalamic region results in memory impairments but also deficits of executive functioning, especially if damage is sustained to the ILn (Bogousslavsky et al, 1988; Daum & Ackerman, 1994b; Mennemeier et al, 1992; Van der Werf et al, 1999). For example, Van der Werf and colleagues describe the neuropsychological impairments of a patient who suffered unilateral damage in the region of the right intralaminar nuclei. These authors reported that the patients showed a conspicuous slowness, inflexibility and lack of concentration in addition to anterograde memory deficits, including an inability to recall words, recognize faces and draw a figure from memory (Rey Osterrieth Complex Figure test). Rather than suggesting a diagnosis of an amnesic syndrome, Van der Werf and colleagues concluded that the memory disorder was secondary to deficits of executive functioning (Van der Werf et al, 1999).

There are discrepancies in the neuropsychological deficits associated with damage to the ILn, but this variability may be explained by the differences in prominent neural connections between the rostral grouping and the caudal grouping of the ILn (see Chapter 6 for further details). Damage to the caudal grouping (centre median and parafascicular nuclei) of the ILn is typically associated with Parkinson's disease (Henderson et al, 2000a, b) and many researchers do not associate these caudal ILn nuclei with memory impairments (Mennemeier et al, 1997).

Infarct damage can also affect neural pathways that traverse this region, in particular the mammillothalamic tract (MMT) and the lateral internal medullary lamina (L-IML). Many researchers have proposed that the neural basis of diencephalic amnesia is the result of damage to either one or both of these pathways, that is, the amnesia caused following fibre tract damage is the result of a disconnection syndrome (Graff-Radford et al, 1990; Markowitsch, 1988; Savage, Sweet, Castillo, & Langlais, 1997; Van Cramon et al, 1986; Van der Werf, et al, 2000; 2003). The MMT connects the mammillary bodies with the AT and in a recent meta-analysis of thalamic infarcts that have caused memory impairments, Van der Werf and colleagues (2000) propose that disruption to this fibre pathway results in the profound amnesic syndrome associated with thalamic amnesia. On the other hand, the L-IML also traverses the thalamus and has projections between many structures of the limbic system and thalamus. In addition the L-IML and MMT run alongside of each other in the region of the ventral anterior thalamic nucleus. Graff-Radford and colleagues (1990) proposed that both the MMT and L-

IML are implicated in thalamic amnesia. In their investigations of two patients who developed severe amnesia following very small lesions in the region of the ventral anterior nucleus of the thalamus, they concluded the amnesia was the result of disruption to both the MMT and L-IML fibre tract pathways.

As yet no clear-cut conclusions can be drawn from the clinical evidence of thalamic infarcts as to the neural basis for thalamic amnesia.

4.4 Prion Diseases and Thalamic Amnesia

There are a number of fatal disorders of the nervous system caused by mutant prions. The function of the prion protein and the pathogenetic mechanisms of the neural damage in the diseases remain unclear. Currently though it is hypothesised that the prion proteins when mutated or by a spontaneous process, become unstable and convert into protease-resistant forms, which then act as templates for similar conversion of physiological prion proteins. The cell is unable to break down the mutant proteins. These prion diseases are all associated with substantial mutant prions affected cells in the thalamus (amongst other brain regions too) and the neuropathology associated with memory impairments is discussed below.

4.4.1 Variant Creutzfeldt-Jakob disease (vCJD)

The variant form of Creutzfeldt-Jakob disease manifested in humans is causally linked to bovine spongiform encephalopathy (BSE) and was first diagnosed as such in 1996 (Collins et al, 2004). This variant form of the disease presents as a predominantly psychological disorder with additional cognitive difficulties, whereas the other sporadic and genetic forms of CJD typically only have cognitive difficulties, e.g. disturbances of language, vision, hearing and executive functioning (Kapur et al, 2001, 2003). The early features of vCJD do not typically include neurological features. However, by 4-6 months of the disease progression, patients suffer from poor memory, impaired concentration and aggression (Will et al, 2000; Spencer et al, 2003). In a clinical case study of Kapur and colleagues (2001), their patient had memory difficulties as an early feature. It is proposed that the memory impairments were not in the amnesic range, that is, they were less severe deficits than those apparent in amnesic KS patients. The cause of the memory impairments was attributed to the extent of mutant prion

proteins present in the medial, lateral and pulvinar nuclei of the thalamus causing neuronal loss (Kapur et al, 2001, 2003).

4.4.2 Fatal familial insomnia (FFI)

This prion disease disorder can be either sporadic or hereditary and it is infectious. There are many clinical manifestations of the disorder with sleep disturbances being most markedly disrupted. The main neuropsychological changes include progressive disturbance of attention and vigilance associated with deficits in working with and the lability of memory. In addition, patients have difficulty with temporal ordering of events. Some other frontal-lobe functions are also impaired, including planning and forecasting of events. Patients do not suffer a decline in general intelligence. As is the case with vCJD, patients with FFI exhibit memory problems but they cannot be diagnosed with an amnesic syndrome due to the other cognitive problems, rather FFI is more akin to a progressive confusional state (Montagna et al, 2003).

The most consistent neuropathological features of FFI are severe changes in anterior ventral and MDn thalamic nuclei, with from 50% and up to 80% in some cases of neuronal loss in the magnocellular and parvicellular regions of the MDn (Montagna et al, 2003). Severely reduced use of glucose in the thalamus and degeneration of the inferior olivary nucleus were confirmed as the early indicator of FFI and additional cerebral and cerebellar involvement may be the consequence of the long disease course in some patients although there is no consistency of atrophy in these regions.

This neuropathological evidence from the prion diseases further suggests a role for the thalamus in memory impairments and in other aspects of cognitive functioning including attention, arousal, and changes in mood.

4.5 Other Neurodegenerative and Psychological Disorders

There are neuropathological studies implicating brain damage in the medial thalamus, in particular the mediodorsal and anterior nuclei, in schizophrenia, although the results are mixed (Byne et al, 2002). The specificity of the findings is difficult to assess since the definition of the disorder, the clinical evolution, the time spent in psychiatric hospitals, neuroleptic

therapies, the circumstances of the death and many technical artefacts related to shrinkage, fixation, staining etc are likely to modify the results (Macchi, 1997).

Neurodegenerative diseases associated with tremors due to multiple sclerosis, trauma, or stroke or tremor due to Parkinson disease can affect the human thalamus and are typically associated with atrophy of the parafasiscular complex and centre median thalamic nuclei, namely the caudal intralaminar nuclei (Diederich et al 1992; Krauss et al, 2002; Henderson et al, 2000a, b). Recent neuropathological studies of Parkinson's disease patients have reported reductions in these caudal intralaminar regions of the thalamus but found no associated between this atrophy and memory deficits (Henderson et al, 2000a, b, 2001).

Finally, in the progression of Alzheimer's disease, there is damage in many brain regions of the limbic system including the anterior thalamic nuclei, especially the early degeneration of the anterodorsal sub-nucleus of the AT (Braak & Braak, 1991, 1998; Johnson et al, 1998).

4.6 Current Theories of Medial Diencephalon Involvement in Memory

It has been suggested that the types of memory deficits suffered by diencephalic amnesics and MTL amnesics are qualitatively and quantitatively different (Parkin and colleagues, 1992; 1997). Parkin proposed this notion based on assessments of KS patients and Herpes simplex encephalitis affecting MTL regions and hippocampus. In the brief review presented above of the cognitive, behavioural and memory impairments demonstrated by KS patients, it is apparent that in some aspects KS patients are different to MTL damaged amnesics. However, there are also many similarities in memory impairments and also in relation to other aspects of medial thalamic brain injury, therefore the clinical and neuropathological evidence presented above suggests that aspects of this notion proposed by Parkin et al (1997) should be revised.

Instead, Aggleton and Brown (1999) suggested an alternative perspective about the involvement of medial diencephalic structures in amnesia. Rather than suggesting that the two brain regions function separately, Aggleton and Brown have proposed that independent circuits, comprising of different structures of the medial diencephalon interconnected with different regions of the medial temporal lobes, work together in declarative memory processes. This proposal is based on the notion that pathology in either the medial temporal lobes or the medial diencephalon can lead to similar amnesic syndromes (Aggleton & Brown, 1999). One independent circuit of interconnected structures, an 'extended hippocampal system',

comprising of the hippocampus, the fornix, the mammillary bodies, and the anterior thalamic nuclei, was originally proposed by Delay and Brion (1969, cited in Aggleton & Brown, 1999). This extended hippocampal system is proposed to be responsible for episodic declarative memory processes, namely efficient encoding and normal recall of new episodic information. Damage to structures within this circuit is believed to produce the core deficits in anterograde amnesia. In animal models of amnesia, the extended hippocampal system underlies spatial memory processing (Aggleton & Pearce, 2001; Gaffan & Parker, 2000).

Aggleton and Brown's (1999) proposed model of episodic memory processing involving this hippocampal-anterior thalamic circuit suggests that the hippocampal efferents projecting to the medial diencephalon are vital for normal hippocampal activity and are a functional extension of the hippocampus proper. Within the circuit the anterior thalamic nuclei are the principal target because these nuclei receive direct hippocampal projections via the fornix, and indirect hippocampal projections via the mammillary bodies and the mammillothalamic tract (further details of the prominent connections of these structures are provided in Chapter 6). Other important structures in the system are the prefrontal, cingulate and retrosplenial cortices. It is also suggested that the laterodorsal and rostral midline thalamic nuclei may contribute to the system (Aggleton & Brown, 1999; Aggleton & Sahgal, 1993).

Patients with anterograde amnesia caused by damage to the medial diencephalon and / or the medial temporal lobes can also suffer deficits in recognition memory, which Squire and colleagues have proposed is an elemental form of declarative memory (Broadbent et al, 2002; Squire & Knowlton, 1995). Scoville & Milner (1957) suggested that the hippocampal damage was the locus of both episodic and recognition memory deficits suffered by H.M.. However, recent animal lesion models (in both monkeys and rats) have suggested other regions of the medial temporal lobes, adjacent to the hippocampus, may be more critical for recognition memory processing per se. It must be noted that recognition memory may involve at least two independent processes, only one of which is hippocampal dependent (Mandler, 1980; Brown & Aggleton, 2001). In relation to recognition memory then, Aggleton and Brown (Aggleton & Brown, 1999) suggested that the 'extended hippocampal system' is not vital for familiarity judgments of recognition memory. Rather, they proposed another independent parallel circuit of interconnected medial diencephalic and medial temporal lobe structures involving the perirhinal cortex of the temporal lobes and the MDn is involved with familiarity-based recognition memory. Therefore, Aggleton and Brown note that although the hippocampus and

perirhinal cortex are anatomically linked, it appears that they are not necessarily dependent on each other for their respective roles in the encoding of episodic information and familiarity based recognition. That is, these two parallel temporal–thalamic systems are suggested to have qualitatively different contributions to learning and memory processes that can be dissociated from each other if only one circuit is damaged, while damage to both circuits will result in severe deficits in both recall and recognition memory.

Finally, Aggleton and Brown propose that the prefrontal cortex (PFC) plays a vital role by interacting with both episodic and familiarity-based systems of declarative memory. These authors suggest that the role of the PFC intervenes on a variety of levels, thus engaging efficient encoding strategies that can aid subsequent recall. Furthermore, Aggleton and Brown indicate that these two independent systems do not account for all aspects of memory and impairments. Rather they suggest that most amnesics normally have damage to other cortical and sub-cortical structures, which can impact on other aspects of memory and may help to explain some of the variability of individual patient deficits.

Aggleton and Brown's (1999) proposals have caused further debate amongst researchers in the literature. In particular the proposal of the connections between the perirhinal cortex and mediodorsal thalamic nucleus forming a circuit that is implicated in familiarity-based judgments of recognition memory has proven contentious (e.g. Markowitsch, 1999; Parker et al, 1999; Witter et al, 1999). These authors all agree that the perirhinal cortex contributes to recognition memory but the role of the MDn remains uncertain and it is reported that the connections between the perirhinal cortex and MDn are fairly sparse. Furthermore, the evidence in the clinical cases of deficits in recognition memory following damage in the MDn thalamic nucleus is mixed, with some researchers reporting no such impairments (Edelstyn et al, 2002; Shuren et al, 1997).

In addition Aggleton and Brown's proposal does not account for amnesia resulting from lesions affecting the midline and intralaminar (ILn) nuclei or lateral internal medullary lamina, which are all located in the areas of thalamus that have been associated with the occurrence of amnesia (Mair, 1994; Mair et al, 1979; Mennemeier et al, 1992; von Cramon et al, 1985). An alternative possibility proposed by Mair and colleagues (1998, 1999; Burk & Mair 2001a, b) suggests that the ILn also contribute to memory processing. These authors have indicated that the ILn is the most important medial thalamic nuclei responsible for thalamic amnesia. Mair and colleagues have raised the profile of the ILn and conducted extensive animal lesion work

investigating the memory deficits following ILn damage (as will be discussed in further detail in Chapter 5). Briefly though, Mair and colleagues have been proposed that following damage in the ILn, thalamic patients and animals display deficits that there are functionally distinct impairments of memory to those associated with other thalamic, hippocampal, and prefrontal pathology (Mair et al, 1999). That is to say, that it is proposed that the ILn are important to memory processes, but not in accord with the proposals that thalamic amnesia is essentially an extension of hippocampal or prefrontal cortical damage.

Other researchers, for example Van der Werf and colleagues (1999, 2000, 2002, 2003a, b), propose further alternate theories regarding the involvement of the medial thalamus in memory impairments. Van der Werf and colleagues note that within the region of the anterior and medial portions of the thalamus, dissociable contributions to memory can be found. These dissociations are proposed to show that the different nuclei do not play a similar or global role but rather that each nucleus or set of nuclei has a separate function and thus the term diencephalic amnesia may not necessarily be accurate. For example, with regard to the role of the AT in memory processes, Van der Werf and colleagues (2000, 2003) are generally in agreement with the proposal of Aggleton and Brown (1999) except Van der Werf et al include recognition memory deficits of any kind. Van der Werf et al (2000) propose that disruption to the MMT causes the memory impairments associated with the amnesic syndrome suffered by thalamic amnesic. In contrast, Van der Werf et al (2000) suggest that the other thalamic nuclei are involved in other memory and executive functioning deficits. Specifically the midline nuclei and ILn appear to have a role in frontal cognitive functions, with clinical data suggesting they are capable of influencing PFC functioning, whereas the MDn is proposed to have a role in executive functioning, which is also proposed by an intact PFC (Fuster, 2001; Goldman-Rakic, 1995). Although Van der Werf et al indicate that impairments in executive functioning do not have a one-to-one basis with MDn lesions as they can be found in the absence of MDn injury and vice versa.

More recently, Van der Werf and colleagues (2003) suggest that the anterior and medial divisions of the thalamus each contribute a functional role in declarative memory processes. Rather than the MDn and ILn thalamus nuclei especially acting solely as a relay station for cognitive functions, it is proposed that there are specific roles for the contributions of the medial thalamus to declarative memory processing. As Van der Werf et al have previously proposed a lesion to the AT or afferent white matter tract, MMT, results in deficits in encoding

new stimuli. Lesions to the MDn affect executive processing pertaining to declarative memory, such as the use of memory strategies for retrieval, whereas damage to the ILn and midline nuclei result in decreased arousal and thus affects the declarative memory process. The authors propose that the different nuclei of the thalamus play different roles at varying levels of declarative memory functioning, namely the anterior and mediodorsal nuclei are involved in processing the contents of the stimuli for storage and recall. The AT influence the selection of material to be stored and remembered, whereas the MDn are involved in the coordination and selection of strategies used to retrieve material. The ILN and midline nuclei on the other hand maintain a necessary state of arousal amongst the cortical regions involved in the ongoing memory processes. These two groupings of nuclei work in parallel to mediate and allow memory functioning.

In addition, Van der Werf et al (2002) have recently hypothesised further differential roles in declarative memory to the ILn and midline nuclei based on their distinctly different patterns of afferent and efferent projections. That is to say four different groupings of ILn and midline nuclei have been identified, a dorsal group proposed to play a role in viscerolimbic functions; a ventral group that might influence processing of different sensory modalities; a lateral group involved in executive aspects of memory and other forms of cognition; and a posterior group involved in motor responses to emotionally or motivationally significant stimuli.

Another theory (based on work in animals) proposed by Gabriel (1993) suggests how the AT and MDn are involved in memory processes during learning of discriminative active avoidance tasks in rabbits, which offers an alternative theory to the proposal of Aggleton and Brown (1999). Gabriel reports that the AT and MDn and their respective cortical networks (posterior and anterior cingulate cortical areas, respectively) act in a cooperative manner but are differentially involved during the acquisition and maintenance of learned behaviour as indicated by learning-relevant neural circuit activity.

Gabriel's proposal, which is based on electrophysiological recordings of neurons in the medial thalamus and cingulate cortices, appears to indicate that both medial thalamic regions are involved in processes of learning and memory but just at different stages. For example, the system comprising of the MDn and anterior cingulate cortex is involved in the initial stages of learning, while electrophysiological changes in neuronal activity in the AT and posterior cingulate cortex system are not observed until late in training, suggesting that this system is

involved in the maintenance of the learned acquisition even after more recent information has been obtained (Gabriel, 1993). More recent multi-unit neuronal recordings of anterior cingulate cortex and interconnected MD thalamic nucleus neurons in rabbits suggest that these neurons have fundamentally similar functions during both avoidance and approach learning paradigms (Freeman et al, 1996). During avoidance learning tasks, it is noted that MD and anterior cingulate cortex neurons are not activated concurrently, as they are in approach learning tasks. This discrepancy is proposed to be due to the additional contributions of amygdaloid complex neurons during the avoidance paradigms (Freeman et al, 1996).

Gabriel's proposals of AT and MDn thalamic nuclei involvement in learning and memory offer an interesting alternative to the neural basis of thalamic amnesia, the theory does not appear to include a role for the ILn or midline thalamic nuclei.

Therefore, while theories based on clinical evidence in humans and animal lesion models have provided substantial contributions to our understanding of thalamic amnesia, as yet clear double dissociations have not been established between the different medial thalamic nuclei across behavioural memory tasks, so that more reliable conclusions can be drawn about the specific involvement of these medial thalamic regions in memory. The following chapter details the contribution of animal lesion models of thalamic amnesia. The medial thalamic involvement in memory is clearly evident and deficits produced typically parallel the clinical literature, however the neural basis of thalamic amnesia thus far remains inconclusive.

Chapter 5

Animal Models of Diencephalic Amnesia and Experimental Thalamic Lesion Data

As indicated in the previous chapter, the functional contributions of the individual medial thalamic nuclei to memory remain somewhat unclear. Therefore, it is important to progress with animal models of experimental lesions in the various regions of the medial diencephalon to help delineate more clearly their functional contributions to memory processing. This chapter reviews behavioural experiments that have tested animals to determine the role of the medial thalamus in diencephalic amnesia thus far.

5.1 Introduction

Within the past two decades progressively more research has been conducted to establish the specific forms of memory deficits suffered following damage to the medial diencephalon. As indicated in the previous chapter, limitations in the clinical evidence have forced revisions in the approaches used to determine a specific diencephalic structure whose damage leads to the profound amnesic state associated with brain injury to this region.

Animal models are a useful way to overcome some of the limitations inherent from the clinical evidence. The rat is the most commonly used experimental animal for behavioural neuroscience studies and most of the basic anatomical connections between the subcortical and cortical structures of rats are similar to those in monkeys. In addition, over the past few years, memory research has linked the work with rats with the work of humans and non-human primates to a greater degree (Aggleton & Brown, 1999; Aggleton & Pearce, 2001; Gaffan, 1992, 1994; Kesner, 2000; Morris, 2001; Uylings, Groenewegen & Kolb, 2003).

There are many advantages to developing animal models of memory processing. Post-mortem detail is available in animals, which is seldom possible in human cases. Surgical lesions in animals can normally be somewhat more circumspect and involve subtotal, complete or even contra-lateral neuronal damage to connected structures. These planned lesions, if

produced with a high degree of selectivity to the target structures of interest, can encourage a greater degree of certainty about identifying the critical locus and also the particular kinds of memory deficits than are evident in comparative human cases. In addition, direct comparisons are possible between control and lesion animals within pre- versus post-operative testing, across the effects of placebo and drug infusions, or between subtotal lesions to one structure verses another nearby structure.

Despite the benefits of experimental thalamic lesions, animal studies have, like the clinical evidence, also suffered difficulties and produced conflicting findings about the critical locus of thalamic amnesia. Conflicting findings have resulted from utilisation of different techniques to create lesions in the brain, differences in the size and location of these lesions, and the extent of atrophy to surrounding target structures due to the inherent complexity of the medial and 'non-specific' regions of the thalamus. Standardization of memory tasks and testing procedures for animals has also met with difficulties. Nevertheless, it is widely accepted that some tests of spatial working and reference memory provide adequate measures of animal memory that are analogous to human episodic recall tasks (Aggleton & Pearce, 2001; Gaffan, 1994).

The following review of animal models of memory in relation to diencephalic amnesia focuses on the specific thalamic nuclei of interest in the present thesis, that is, the anterior (AT), mediodorsal (MDn), and intralaminar (ILn) thalamic nuclei. It will begin by focusing on the MDn as influential conclusions in the clinical evidence (Victor et al, 1971) directed initial experimental animal research to study lesions centred on this thalamic nucleus. However, the lack of deficits in spatial tasks (e.g. episodic–like declarative memory) following MDn lesions across a variety of different studies prompted a re-evaluation of the evidence, which led to a shift in the focus for experimental thalamic lesions in animals. The lesion sites have now incorporated the AT, ILn and midline thalamic nuclei as well, amongst other diencephalic structures.

5.2 Experimental Mediodorsal Thalamic Nuclei Lesions

This section briefly reviews research that has explored the effects of lesions in the MDn and assesses their impact on performance during memory tasks. A detailed summary of the studies involving MDn thalamic lesions in memory tasks over the past 20 years is provided in Table 1 (p. 54-56).

Table 1. Summary of Studies involving MDn Thalamic Lesions with Assessment of Performance in an array of Memory Tasks during the past 20 years.

Year	Authors	Lesion/Size/Species/Type	Extra Damage	Behavioural Tasks	Training	Delay	Deficits reported
2003	Corbit, Muir & Balleine	MDn, AT S – rats: NMDA	No extra damage was sustained	Instrumental conditioning Devaluation extinction tests	Post-op		Both acquired conditioning, MDn= deficit in selective devaluation effect during extinction
2001	Alexinsky	AT, MDn, RSC, PPC ? – rats: Ibotenic, excision	No exact details given	3/8 baited Radial Maze (working and reference) New Route – Pre-exp- Y/N Contextual Light Change	Pre-op		MDn= less correct visits only; AT= more incorrect reference / working memory visits Pre-exposure -Y= RSC, MDn, AT deficits; - N= PPC, MDn, AT AT= most repetitive errors, others adapted
2001	Chudasama, Bussey & Muir	AT, MDn, PL S – rats, NMDA	MDn: some PV AT: midline, slight dentate gyrus	Visual discriminations and reversals using touch-screen VDU	Pre-op & Post-op		MDn = impaired at reversal of all three visual discriminations, AT and PL similar to controls
2000	Gaffan & Parker	Entire Magnocellular MDn (aspirator) L – monkeys	Fornix	Visual scene memory Object-reward associations	Pre-op Pre-op		Yes Retention= No New Post-op Learning= Yes
1999	Floresco, Braaksma & Phillips	Expt 1: Bilateral MDn Lidocaine Inf. S – rats Expt 2: Contra-lateral MDn / PL of PFC, MDn / N.Acc.	Additional spread of inf not included in analyses Medial Shell of Acc.	Delayed Radial Maze and Pre-training vs pre-test Inf Non delayed random forgaging Radial Maze Delayed Radial Maze and Pre-test Inf only	Post-op Post-op Post-op	30 min 30 min	Pre-training unimpaired. Pre-test infusion severe deficits. Not impaired. MDn/PL of PFC impaired, with more within-phase errors than across-phase errors. MDn/N Acc. not impaired. A PL/N Acc. group were also impaired.
1999	Kornecook, Anzarut & Pinel	PRC, MDn L – rats Electrode	PRC: Entorhinal, CA1 & CA3, Te2 MDn: PVA, PC, PT, CM, Hb, AV, AD	Visual object discrimination, retrograde testing Visual object discrimination	Pre-op Post-op	58,37,169, 2 days prior	PRC= deficits at tasks learnt 2 and 9 days prior to surgery No deficits
1998	Zhang, Burk, Glode & Mair	Expt 1: Pyriform, Entorhinal, L-IML, MDn, PC-CL: NMDA Expt 2: ILn (PC, CL, CM), MDn, all NMDA L – rats	Similar lesion damage to other thalamic nuclei as reported below	Go/no-go DNMTS for odorants Olfactory discrimination learning	Pre-op	4, 6, 9, 13.5, 20.25s	Only pyriform and L-IML performed poorly; pyriform delay independent deficits. Only L-IML were impaired in learning the discrimination ILn lesion produced substantial and consistent deficits, MDn was smaller and more transient; no group was impaired on the olfactory discrimination learning task
1998	Burk & Mair	L-IML, ILn, MDn L – rats: NMDA	L-IML: AT, MDn, PF, VL ILn: AT, MDn, LD, LP, PF, Po, VL, VM, VA MDn: CL, PC, VL, VM	Place DMTS, operant boxes Serial reversal learning	Pre-op, 75% correct	FR2 or 7 1, 3, 8, 13s	ILn lesion significantly impaired, L-IML slightly impaired and remained consistently impaired 8 months after surgery All able to perform reversal but ILn did make slightly more errors (n.s.)

Table 1 (cont). Summary of Studies involving MDn Thalamic Lesions with Assessment of Performance in an array of Memory Tasks during the past 20 years.

Year	Authors	Lesion/Size/Species/Type	Extra Damage	Behavioural Tasks	Training	Delay	Deficits reported
1998	Hunt & Aggleton	Expt 1: MDn L – rats: NMDA Expt 2: MDn L – rats: NMDA	Medial LD, AD, caudal AV, PVA, PT LD, AD, AV, PVA, PT	Standard Radial maze Radial Maze (45° rotation) T-maze Alt 8-arm Radial Maze (Reference vs Working) Spont Object Recognition	Post-op Post-op 	60 s 60 s 10 s 15, 60 min	No Yes, failed to overshadow intramaze with spatial extramaze cues No Yes, both reference and working memory deficits exacerbated by AT damage No
1998	Hunt & Aggleton	MDn L – rats: NMDA	AD, PVA, PT,	8-arm Radial maze conditioned cue preference Exploratory Activity T-Maze MTP T-Maze Reversal	Post-op 	 10 – 40 s 	No No Yes, slower to acquired task but no additional delay deficits No, but MDn more perseverative errors than controls
1996	Peinado-Manzano & Pozo-Garcia	MDn L – rats	Damage to 89% of MDn and part of PV	Delayed alternation in operant boxes	Pre-op	0 – 40 s and 80 s	Moderate and transient impairment for 0 – 40 s and severe impairment for 80 s
1996	Young, Stevens, Converse & Mair	L-IML MDn Fornix L – rats: RF	L-IML: MDn PC, CL, MDpl, tracts to PFC MDn: PV, only one plate, no detail in text.	DNMTS in operant boxes 8-arm Radial Maze	Pre-op Post-op	1.8s – 8.8s	L-IML group more impaired than others, although all worse at greater delays L-IML, MDn and fornix lesions all produced deficits in acquisition of the radial maze task.
1995	Krazem, Beracochea & Jaffard	MDn, MB L – mice: Ibotenic acid	MDn: CM, midline	T-Maze Spatial Repetition T-Maze Reversal	Post-op	5 min, 24 hr	No Yes, both MB & MDn= more trials required
1994	Neave, Lloyd, Sahgal & Aggleton	MDn (NMDA), FX (RF) L – rats	Damage to 80% of MDn, medial LD, PV, caudal AM / AV in 3 rats	Object, concurrent and configural discriminations	Post-op		FX lesion quicker to learn 1st discrimination than MDn and controls. FX & MDn mildly impaired on concurrent and FX impaired at configural discrimination
1993	Gaffan, Murrau & Fahre-Thorpe	Crossed unilateral lesions to Amyg and contra-lateral MDn and VM PFC ? – monkeys		2-choice visual discrimination task with food reward for correct choices	Post-op		The crossed unilateral Amyg and contra-lateral MDn and VM PFC caused severe deficits in post-op acquisition, which were comparative to bilateral leions to either Amyg, MDn, or VM PFC as reported previously.
1993	Mumby, Pinel & Dastur	MDn L – rats: Electrolytic	AD, AM, AV, PVA, PT, PC, CM, Hb, dentate gyrus	Visual object recognition DNMS	Post-op Pre-op	4 s acq. 30-300 s 4 –300 s	Yes, more trials to learn, then delay dependent deficits 30- 300s Yes, more trials to reacquire
1993	Neave, Sahgal & Aggleton	L- rats NMDA	Damage to 72% - 100%, PV, PT, medial LD	DNMTP Spatial Discrim & Reversal	Post-op	0 – 32 s	No No
1991	Hunt & Aggleton	MDn L – rats RF & Ibotenic acid		Y-Maze Object Recognition T-Maze Delay Alt	Post-op	0,20,60s 10,30,60s	Yes Yes, spatial memory deficits only a consequence of anterior thalamic involvement

Table 1 (cont). Summary of Studies involving MDn Thalamic Lesions with Assessment of Performance in an array of Memory Tasks during the past 20 years.

Year	Authors	Lesion/Size/Species/Type	Extra Damage	Behavioural Tasks	Training	Delay	Deficits reported
1991	M'Harzi, Jarrard, Willig, Palacios & Delacour	MDn Electrolytic	Behav Neural Biol. 1991 Nov;56(3):221-35	Radial Maze Place Recognition Object Recognition	Post-op		Yes No No
1991	Peinado-Manzano & Pozo-Garcia	AT, MDn L - rats Electrolytic	MDn: 90% damage, PV AT: 89% to AT, also PV, PT, rostral MDn	Operant Delay Alt	Post-op	0 – 80 sec	Yes, both groups significantly impaired.
1990	Gaffan & Murray	MDn, VM PFC, Amyg Crossed unilateral to MDn + Amyg , VMPFC +Amyg ? - monkeys		2-choice visual discriminations with food reward for correct choices	Post-op		All bilateral lesions to MDn, VM PFC, and amygdala impaired Crossed unilateral lesions not as impaired as bilateral lesions to any of the single regions.
1990a	Stokes & Best	MDn L - rats Electrolytic		8-arm Radial Maze (working & reference)	Post-op		Yes
1990b	Stokes & Best	L – rats Ibotenic	AD, CM, IMD, Hb, LD, PT, PVA,	8-arm Radial Maze (serial position)	Post-op		Yes
1989	Beracochea, Jaffard & Jarrard	M Ibotenic		8-arm Radial Maze T-Maze Temp Alt T-Maze Spatial Reversal	Post-op	 15, 45 s	No Yes = 15 s but not with 45 s delay No
1988	Stokes & Best	MDn L – rats Electrolytic	AT, Hb, CL, CM, PVA, PC, PT, Re,	8-arm Radial Maze	Pre-op	0 s	Yes
1985	Zola-Morgan & Squire	Posterior MDn L – monkeys Electrode	Fornix, CM, Hb, PF, PVA	Visual DNMTS Pattern Discrimination	Post-op	8, 15, 60 s, 10 min	Yes, delay independent No, analogous to preserved capacity for skill learning in human amnesic patients
1985	Winocur	MDn, dHPC ? – rats		Delayed alternation Passive Avoidance		0 – 80 s 1 hr – 21 d	MDn impaired on delayed alternation but not passive avoidance dHPC = delay-dependent impairment

Abbreviations:

Alt.= Alternation, Amyg= amygdala, Contra = Contra-lateral, dHPC= dorsal hippocampus, Egocentric = Egocentric Discrimination, FF= Fimbria-fornix; FX = Fornix, Ipsi = Ipsi-lateral, L= Large FX= fornix, Hb= habenula, L= Large, M= Medium, RF= radiofrequency, S= Small, Seq. = Sequential, Spont. = Spontaneous, post-op = post-operative, pre-op = pre-operative, VM PFC= ventromedial PFC, ?= not clear indication of lesion size. For other abbreviations see elsewhere in dissertation.

Although early studies that assessed the effects of MDn lesions in memory tasks found significant deficits in memory during performance in spatial tasks, further studies have not replicated these initial findings. Stokes & Best (1988, 1990a, b) reported significant deficits in both spatial working and reference memory components of a radial arm maze task after large, complete lesions to the MDn (and consequently, adjacent nuclei). However, these findings were not replicated when subsequent studies using more restricted MDn lesions failed to produce impairments in spatial working or reference memory processing (Hunt & Aggleton, 1991; 1998a, b; Kolb, Pittman, Sutherland & Whishaw, 1982; Neave, Sahgal & Aggleton, 1993), although see Young et al (1996). The large MDn lesions of Stokes and Best encroached into the AT thalamic nuclei, which Hunt and Aggleton (1991) suggested produced the deficits in working memory amongst the animals tested. Further investigations of lesions to the MDn and impairments at spatial memory suggest that MDn lesions alone are inadequate to affect episodic-like memory processing on spatial memory tasks.

In contrast to spatial memory processing, the MDn may play a role in recognition memory but thus far the evidence is mixed. Several studies have reported deficits in both acquisition and performance of delayed matching-to-sample (DMS) and delayed non-matching-to-sample (DNMS) object recognition using both rats and non-human primates (Aggleton & Mishkin, 1983; Eascott et al, 1997; Gaffan & Parker, 2000; Hunt & Aggleton, 1991; Mumby et al, 1993; Parker et al, 1997; Zola-Morgan & Squire, 1985), while others have reported no deficits on various recognition tasks (e.g. Hunt & Aggleton, 1998; Kornecook, Anzarut & Pinel, 1999; M'Harzi et al, 1991).

Additionally, we know that a single region of the brain does not act alone, but rather depends on interconnections with other regions. It has been proposed that the MDn lesions may disrupt connections with the prefrontal cortex (PFC) and that this disruption causes memory impairments. The PFC is associated with higher order cognitive functioning, often labeled 'executive functioning' in humans. It has been suggested, therefore, that lesions to the MDn could disrupt pathways leading to the PFC and may affect processes that are typically governed by the PFC, including attention, inhibition, planning, coordination and strategy selection, which could produce memory impairments on tasks. Researchers have observed in rats with MDn lesions certain behavioural deficits that could result in memory impairments, for example, an inability to adopt different strategies, or changes in activity and exploration levels or deficits in withholding spatial responses (Alexinsky, 2001; Hunt & Aggleton, 1991, 1998b).

Additionally, in a recent study, Floresco and colleagues (1999a, b) used a spatial delayed responding task to suggest that the interaction between the PFC and the MDn mediates 'context-dependent retrieval and manipulation of recently acquired information'. Thus it was proposed that the cause of the deficient memory performance following MDn damage was the result of disruptions in the use of memory strategies governed by the PFC. Furthermore Floresco et al (1999) propose their findings are consistent with the theoretical model of discriminative learning proposed by Gabriel (1993) and Freeman et al (1996), which was outlined in Chapter 4.

Disruptions to other prominently connected regions of the MDn, for example the amygdala, have not been fully investigated. Some evidence may suggest impairment of MDn lesion rats, but not AT lesion rats, in stimulus-reward type associative learning (Corbitt et al, 2003). Corbitt and colleagues assessed the effect of highly selective MDn and AT lesions in several tests of instrumental conditioning, namely 'acquisition of instrumental performance, sensitivity to outcome devaluation by specific satiety, and sensitivity to selective degradation of the action-outcome contingency'. MDn and AT lesions rats were both able to acquire the instrumental performance but during the degradation of the action-outcome contingency test, the MDn lesion rats were unable to demonstrate reliable devaluation effects. This deficit shown by the MDn lesion rats was dissociated from the AT lesion rats and controls, which did not differ and suggests the MDn contributes to deficits in encoding and / or utilizing the action-outcome association (Corbitt et al, 2003).

Dissociable deficits between the MDn and AT have also been reported (Chudasama & Muir, 2001; Chudasama et al, 2001). For example, Chudasama and Muir (2001) assessed the behavioural effects of lesions to the MDn and AT using the five-choice serial reaction time task and a vigilance task. These authors reported no deficits in attentional performance following AT lesions. In contrast, the MDn lesions caused rats to increase anticipatory responding during baseline performance and when the inter-trial interval was varied randomly during the serial reaction time task. MDn lesions did not produce deficits in the vigilance attention task.

Dissociable deficits between the MDn and ILn have also been reported (Burk & Mair, 1998; Young et al, 1996). For example, Burk and Mair (1998) assessed the effects of lesions to the MDn, ILn and IML during post-operative performance in a place DMTS using operant boxes. These authors reported no effect to performance following lesions to the MDn. In

contrast the ILn lesion caused severe impairments in correct responses and the IML lesion rats were moderately impaired. This effect of lesion continued eight months after surgery.

Animal models used to interpret the functions of the MDn thalamic nucleus suggest that while the MDn are part of the thalamic region damaged in KS, this nucleus alone is unlikely to produce the profound amnesic deficits in this syndrome. Moreover, it seems likely that the MDn contribution to learning and memory processes is distinct to that of the AT and ILn.

5.3 Experimental Anterior Thalamic Nuclei Lesions

This section briefly reviews research that has explored the effects of lesions in the AT thalamic region and assesses their impact on performance during memory tasks. A detailed summary of the studies involving AT thalamic lesions in memory tasks over the past 20 years is provided in Table 2 (p. 60-62).

Table 2. Summary of Studies involving AT Thalamic Lesions with Assessment of Performance in an array of Memory Tasks during the past 20 years.

Year	Authors	Lesion/Size/Species/Type	Extra Damage	Behavioural Tasks	Training	Delays	Deficits reported
2003	Corbit, Muir & Balleine	MD, AT S – rats; NMDA	No extra damage was sustained	Instrumental conditioning Devaluation extinction tests	Post-op		Both acquired conditioning, MD= deficit in selective devaluation during extinction
2003	Mair, Burk & Porter	AT, PH, AT-PH L – rats: NMDA, RF	AT: CL, LD, PC, PT, rostral MD	Varying-choice DNM spatial Radial Maze	Pre-op	0 – 32 s	All impaired initially then in a delay-dependent fashion across further sessions
2003	Moran & Dalrymple-Alford	AT, PRC L – rats NMDA	AT: PC, LD, CL, Rt	12-arm Radial Maze Spatial Configuration Spont Object Recognition	Post-op	5, 14, 40 min	AT= radial maze deficits Perirhinal= configuration deficits No
2002	Mitchell, Dalrymple-Alford & Christie	AT S – rats Scopolamine Infusion 1, 2.51, 6.31, 10, 15μg	Some fornix, Rt, LD	12-arm Radial Maze – Inf after 6 forced visits. Infusion prior to testing in standard version (doors)	Pre-op	10 min & 5 s RI 5 s RI	Yes, 10 μg infusion increased errors during choice phase to both forced & free choice arms 10 μg= more working memory errors
2002	Van Groen, Kadish & Wyss	AD/AV, AD/AV+, AD/AV/AM S/M – rats; Ibotenic	Extra damage to brain not indicated in study	Water Maze	Post-op	-	All impaired on working and reference memory components, but only AD/AV/AM showed no improvement across trials
2002	Ward-Robinson, Wilton, Muir, Honey, Vann & Aggleton	AT L – rats NMDA	PVA, PT, PC, CL, Re, dentate gyrus	Non-spatial sensory pre-conditioning to fear Conditioned taste aversion T-maze Spatial Forced Alt	Post-op Post-op	-	No, able to acquire sensory pre-conditioning No Yes, impaired
2001	Alexinsky	AT (Ibotenic) MD (Ibotenic) RSC, PPC (excision) ? – rats	No exact details given	3/8 baited Radial Maze (working and reference) New Route – Pre-exp- Y/N Contextual Light Change	Pre-op	-	MD= less correct visits only; AT= more incorrect reference / working memory visits AT, MD, PPC most impaired despite pre-exposure AT= most repetitive errors
2001	Chudasama, Bussey & Muir	MDn, AT, PL S – rats; NMDA	MDn: some PV AT: midline, slight dentate gyrus	Visual discriminations and reversals using touch-screen VDU	Pre-op & Post-op		Dn = impaired at reversal of all three visual discriminations, AT and PL similar to controls
2001	Chudasama & Muir	PL, MD, AT S – rats; NMDA	Slight dentate gyrus	5-choice serial reaction time Sustained vigilance task	Pre-op Pre-op	-	PL= perseverative responding; MD= increased anticipatory responses
2001	Gaffan, Bannerman, Warburton & Aggleton	Expt 1: MB, AT, Expt 2: FX, RH L – rats; NMDA	AT: CL, LD, PC, PT, PVA, Re RH: pre- and para-subiculum, vHPC/CA1	T-maze Spatial Forced Alt Locomotor activity Visual scene discriminations	Post-op	-	Expt 1: AT. MB impaired Expt 2: FX higher activity levels FX, AT, MB deficits= novel objects in same places, and familiar objects and places recombined; RH= no deficits
2001	Warburton, Baird, Morgan, Muir & Aggleton	AT-HPC Ispi, AT-HPC Contra, L – rats; NMDA	Rostral CL LD, MD, PC, PT	T-maze Spatial Forced Alt Water Maze and Probe trial 8-arm Radial Maze	Post-op		Yes, AT-HPC Contra impaired Yes, AT-HPC Contra impaired Yes, AT-HPC Contra impaired
2001	Wilton, Baird, Muir, Honey & Aggleton	AD/LD S – rats; NMDA	AV, AM	T-maze Spatial Forced Alt Water Maze and Probe trial Object-in-place Spont Object recognition	Post-op	- 15 min	Yes Yes Yes No

Table 2 (cont). Summary of Studies involving MDn Thalamic Lesions with Assessment of Performance in an array of Memory Tasks during the past 20 years.

Year	Authors	Lesion/Size/Species/Type	Extra Damage	Behavioural Tasks	Training	Delays	Deficits reported
2000	Celerier, Ognard, Decorte & Beracochea	AT, Alcohol induced M – mice Ibotenic acid (AT)	AT: PVA, PC, PT, CL, LD Alcohol: severe MB, moderate AT, CA1	T-Maze Spatial Forced and Sequential Alt Non-spatial Temporal Alt Auditory and Contextual Fear Conditioning	Post-op Post-op	30, 60 s 15, 30, 60 s	Yes, AT = delay dependent in both while Alcohol = Seq Alt only Yes, AT = delay dependent Yes, AT = both conditions; Alcohol = contextual condition
2000	Warburton, Baird, Morgan, Muir & Aggleton	AT-FX Ipsi AT-FX Contra AT-FX Contra + Hippo M – rats Cyotoxic	Rostral PC, CL, MD, LD, Rt,	Spont Object Recognition Object location (in-place) T-Maze Spatial Forced Alt Water Maze 8-arm Radial Maze T-Maze Alt	Post-op Post-op 	15 min 5 min 10 s 10 s	No Yes Yes Yes Yes Yes
1999	Sziklas & Petrides	AT M – rats; Electrolytic	IAM, partial LD, slight rostral MD, PC, PT, PVA	8-arm Radial Maze Spatial Visual Association T-Maze Visual Egocentric	Post-op	20 s	Yes Yes No
1999	Warburton & Aggleton	AT, FX L – rats; NMDA, RF	PVA, PT, Rostral PC, CL, CM, MD, Re	Water Maze and Probe test T-Maze Spatial Forced Alt Spont Object Recognition	Post-op	 15 s 15 min	Both impaired, AT worse than FX Yes, both impaired No
1999	Warburton, Morgan, Baird, Muir & Aggleton	AT, FX L – rats; NMDA, RF	PT, MD, Re, Rostral CL, CM, PC, Rt, VA	Water Maze & T-Maze	Pre-op Pre-op	- -	Both impaired, but rapidly reacquired Extensive ANT+ damage= permanent deficits in both tasks, loss of the procedural information
1997	Parker & Gaffan	AT, Cingulate L –monkeys; aspirator	AT: midline and VA, fornix, MB	Object-in-place	Pre-op		Yes, both; AT severely impaired
1997	Warburton, Baird & Aggleton	AT, AT + LD, FX L – rats; NMDA RF	Slight Re, rostral MD, PC, CL, CM	T-Maze Forced Alt X-Maze Allocentric X-Maze Egocentric Discrim.	Post-op	0 – 30 s - 10 s	All impaired and delay-dependent Yes, all impaired No
1996	Aggleton, Hunt, Nagle & Neave	AT, AM, AV/AD M/L – rats; NMDA	AT: PVA, PT, Re, Rt, rostral LD, MD, MB shrunken AM: some PT AV/AD: none	T-Maze Forced Alt Allocentric Alt Egocentric Discrimination 8-arm Radial Maze - 90° rotation	Post-op	15 s - 60 s	Yes, AT worse than others Yes, AT worse than others No Yes, AT and AV/AD groups impaired, AM similar to controls
1996	Byatt & Dalrymple-Alford	AV, AM S – rats; RF	Some overlap between sub-nuclei, AD.	12-arm Radial Maze (Working & Reference)	Post-op		Yes
1995	Aggleton, Neave, Nagle & Hunt	AT, MB, FX M – rats; NMDA, RF	AT: CL, LD, PC, PT, PVA, Re	T-Maze Spatial Forced Alt Spont Object Recognition	Post-op	10 - 40 s 1, 15 min	Slower to acquire, delay-dependent deficits No
1994	Berachochea & Jaffard	L – mice; Ibotenic acid		T-Maze Delay Alt T-Maze Seq Alt	Post-op	5 min 6 hours 30 s	No Yes No

Table 2 (cont). Summary of Studies involving MDn Thalamic Lesions with Assessment of Performance in an array of Memory Tasks during the past 20 years.

Year	Authors	Lesion/Size/Species/Type	Extra Damage	Behavioural Tasks	Training	Delays	Deficits reported
1991	Aggleton, Keith & Saghal	Fornix, AT, MB M – rats; NMDA, RF	AT: PT, PVA, PC, CL, Re	Operant DNMTP	Pre-op	>0-32 s 0 s	Yes, fornix & AT impaired No
1991	Beracochea & Jaffard	L – mice Ibotenic & Alcohol		T-Maze Spontaneous Alt	Post-op	30 s	Yes
1991	Peinado-Manzano & Pozo-Garcia	AT, MD L – rats Electrolytic	MD= 90 %, PV AT = 89% AM/AV, also PT, rostral MD	Operant Delay Alt	Post-op	0 – 80 s	Yes, both groups significantly impaired
1989	Beracochea, Jaffard & Jarrard	L – mice Ibotenic acid		T-Maze Temporal Alt 8-arm Radial Maze Spatial Reversal	Post-op	45 s 15 s	Yes No No No
1989	Sutherland & Rodriguez	L – rats Electrolytic	Do not mention	Water Maze (working and reference memory)	Post-op Pre-op		Yes, longer to reach hidden platform No, for same position, Yes for position change

For Abbreviations see Table 1 pg 54-56.

It is proposed that the AT thalamic nucleus plays a role in spatial memory. Researchers, using either permanent or temporary drug induced disruption to the AT, or partial lesions to the individual sub-nuclei have demonstrated substantial impairments in spatial processing across a variety of spatial memory tasks (Aggleton et al, 1991, 1995, 1996; Alexinsky, 2001; Byatt & Dalrymple-Alford, 1996; Celerier et al, 2000; Mair et al, 2003; Mitchell et al, 2002; Moran & Dalrymple-Alford, 2003; Gaffan et al, 2001; Parker & Gaffan, 1997; Peinado-Manzano & Pozo-Garcia, 1991; Sutherland & Rodriguez, 1989; Sziklas & Petrides, 1999; Van Groen et al, 2002; Warburton & Aggleton, 1999; Warburton et al, 1997, 1999, 2001; Wilton et al, 2001). Additionally, it has been reported that extensive pre-training in water maze and T-maze spatial tasks prior to permanent AT lesions does not reduce post-operative memory impairments (Warburton et al, 1999). Another study reported that pre-operative training in the water maze task does ameliorate the effects of AT lesions on post-operative performance (Sutherland & Rodriguez, 1989). Warburton and colleagues suggested the differences in post-operative water maze performance of the two studies was that the former study (Warburton et al, 1999) used a more demanding test of spatial memory processes in the water maze and was therefore more sensitive to lesion-induced deficits. Thus it is suggested that the AT is required for 'on-line processing of spatial information' in addition to its proposed role in acquiring new information (Warburton et al, 1999).

Furthermore, evidence from other types of behavioural memory assessment suggests that the AT does not contribute to egocentric response learning. For example, lesions of the AT did not impair the ability to learn a visuospatial conditional learning task that could be solved by associating specific body turns (e.g. an egocentric response) with visual stimuli (Sziklas & Petrides, 1999). Likewise AT lesions did not disrupt an egocentric discrimination or its reversal; that is, lesions to the AT did not disrupt the ability to acquire an egocentric rule (always turn to the left or to the right) and then to reverse the reinforced turn (Aggleton et al, 1996; Warburton et al, 1997).

It also appears that the AT does not play a role in recognition memory as AT lesions do not disrupt the performance of rats during object recognition tasks (Aggleton et al, 1995; Warburton & Aggleton, 1999). A similar finding is reported in the human clinical literature (Aggleton & Shaw, 1996; Ghika-Schmid & Bogousslavsky, 2000).

Additionally, crossed lesion studies that have induced selective unilateral damage to the AT and also the contra-lateral (opposite side) hippocampus or contra-lateral fornix produces deficits in spatial memory including T-maze, water maze and 8-arm radial maze tasks but not ipsi-lateral (same side) lesions (Warburton et al, 2000, 2001). Warburton and colleagues propose that this evidence provides direct support for the notion that the AT and hippocampus / fornix operate in conjunction within an intergrated neural network during processing of spatial information. In another study, unilateral lesions to the anteroventral (AV) nucleus of the AT do disrupt spatial memory in a 12-arm radial maze task (Mitchell, 2001, pilot study of Masters' dissertation). This study assessed the effects on spatial memory performance in an all arms baited 12-arm radial maze task following a unilateral cannula implant positioned 1 or 2 mm above the AV nucleus and a contra-lateral NMDA lesion into the AV nucleus versus bilateral cannula implants positioned 1 or 2 mm above the AV. Moreover it was observed that the unilateral lesion group continued to show impaired performance in an all-arms baited version of a 12-arm radial maze task following 20 post-operative sessions, whereas bilateral implant rats were slower than controls to acquire the task but had attain a similar performance level as the controls by 17-20 post-operative sessions.

All of this behavioural evidence further confirms the proposal that the AT thalamic nuclei form a nodal point in 'an extended hippocampal system', which is responsible for spatial memory (Aggleton & Brown, 1999). While on the other hand the evidence of AT lesions does not suggest that this region can account for the whole range of memory deficits often associated with diencephalic amnesia. For example, AT lesions do not appear to produce deficits on recognition memory tasks or produce problems in egocentric memory (although the latter may or may not be due to frontal disruption; Holdstock et al, 1999).

5.4 Experimental Intralaminar Nuclei / Internal Medullary Lamina Lesion Models

This section briefly reviews research that has explored the effects of lesions in the ILn thalamic nucleus and internal medullary lamina (IML) pathway and assesses their impact on performance during memory tasks. This section also includes a sub-section (5.4.1), which focuses on a review of the animal pyrithiamine-induced thiamine deficiency (PTD) model used to mimic the effects of chronic alcohol abuse and / or thiamine deficiency in humans in order to assess how these factors influence memory processes. This sub-section is included here because the IML is the most consistently damage medial thalamic region following PTD

treatment, though it must be noted that the AV sub-nucleus of the AT is also affected. A detailed summary of the studies involving ILn / IML thalamic lesions and PTD in memory tasks is provided in Table 3 (p. 66-69).

With regard to experimental lesions in the ILn and IML it has thus far proven impossible to lesion these structures without also often causing substantial brain damage to adjacent areas of thalamus, including portions of MDn, AT and midline thalamic nuclei. Thus far then, conclusions about the memory impairments associated with the ILn are probably less certain than those associated with MDn or AT lesions. In addition, brain damage to the ILn and IML has been induced using two different techniques, that is, both neurotoxic drug lesions and radio-frequency current lesions. These two techniques cause differing degrees of brain damage, which has led to mixed results across studies as radio-frequency lesions also destroy fibres of passage passing through the brain regions of interest.

Nevertheless lesions to the ILn have been found to produce deficits in spatial memory (Burk & Mair, 1998; Mair et al, 1998; Savage et al, 1998; Young et al, 1996). The relationship between the ILn (and also the IML) and memory is supported in the most part from evidence that comparable impairments are not observed on similar tasks after lesions to various other brain structures. That is to say that extensive experimental research has compared the effects of lesions to the ILn or IML with lesions to other structures in the medial thalamus or that are interconnected to these other medial thalamic regions, for example the hippocampus and PFC. The conclusions drawn, from the dissociable effects produced in the memory tasks, are that the ILn or IML are associated with distinct aspects of spatial memory. Within this experimental paradigm, lesions to the ILn and IML have been compared to lesions in the AT, MDn, midline thalamus, dorsal hippocampus, fornix, the mammillary bodies, medial wall of the prefrontal cortex and rhinal sulcus of the cortex across an array of memory tasks, most often delayed matching and non-matching tasks (Burk & Mair, 1998; Mair et al, 2003; Mair & Lacourse, 1992; Young et al, 1996; Zhang et al, 1998).

Table 3. Summary of Studies involving ILn / IML Lesions and the PTD model with Assessment of Performance in an array Memory Tasks over the past 20 years.

Year	Authors	Lesion/Size/Species/Type	Extra damage	Behavioural Tasks	Training	Delays	Deficits reported
2001	Burk & Mair	ILn (PC, CL, CM, PF), HPC (D & V), mPFC L – rats; NMDA RF	ILn: MD, VM, ATN, LD, Po, VL	Self-paced reaction time task	Pre-op 85%		Response accuracy was worse at shorter stimulus presentation times, mPFC= impaired. ILn and mPFC responded at longer latencies.
2001	Porter, Koch & Mair	Unilateral OT & ipsi- or contra-ILn infusion S – rats; Lidocaine		DMS in operant boxes (water reward)	Pre-op 85% ave across delays	1, 3, 8, 13 secs	Slight, dose-dependent Slight, contra-lesion infusion impairment**
1999	Burk & Mair	ILn, VM, LD L – rats; NMDA	ILn: MDl, MDm, medial LD, AV, AD, AM VM: PC, CL, LD LD: MD, AV, AD, VL, Po	DMS in operant boxes (water reward) Serial reversal learning	Pre-op to 80% criterion	1 - 13s & FR 2 or 7 on sample lever 1 - 24s & FR1	ILn= impaired, VMn slightly impaired; all groups performed less accurately at longer delays but improved as the FR went up. ILn & VMn were slower to response than Control & LD. All able to perform but ILn made slightly more errors (though n.s.)
1999	Mumby, Cameli & Glenn	IML, PTD L – rats; Electrolytic (IML), Daily injection of pyrithiamine or saline (PTD)	IML: AM, AV, AD, CM, MDv, MDl, VL; no Po, PF PTD: CM, CL, PC, PF, VL, ventral MD, anterior Po, MB	Water Maze (DMTP) Three object-discrimination problems,	Pre-op / treatment 5-weeks, 3-weeks, 1-week prior to treatment / lesion	4, 60, 300 s	PTD slower on second swim escape latencies and delay dependent deficits No deficits amongst groups Concludes damage to IML pathways or thalamic nuclei from the IML-lesions cannot account for deficits observed in PTD rats, rather PTD-induced deficits occur either from damage outside IML or from combined IML and other area damage
1999	Savage, Pitkin & Knitowski	PTD treatment for 13 - 16 days and IP of scopolamine or MK-801	All IML-spared, some midline nuclei damage but no MB damage	MTP and DMTP in operant boxes	Pre-op	0 – 48 s	PTD-treated rats impaired but not extensive, and scopolamine and MK-801 caused additional dose-dependent impairments in memory. Delays also further impaired performance.
1998	Mair, Burk & Porter	Expt 1: MW of PFC, HPC L – rats; RF	Only intended damage	DMS in operant boxes (water reward) Serial reversal learning Olfactory Continuous DNMS	Pre-op 75% Post-op Pre-op	1 – 13 s and 1 – 24 s	MW impaired accuracy only at shorter retention intervals (1 - 13 s) also slower to respond. HPC not impaired No deficits for MW or HPC
		Expt 2: D & V HPC L – rats RF		Olfactory Discrimination 8-arm Radial Maze		0, 30, 60 s stimulus set size 8 or 16 odorants	HPC, ILn impaired in re-acquisition with no improvement across sessions
		Expt 3: HPC, ILn L – rats; RF, NMDA	ILn: rostral MD, LD, LP, VM	4 forced arms Two-choice DNMS lights on/off x choices vary/recur Water Maze	Post-op Pre-op – all arms baited Post-op	No delay 0, 5, 15 min after 4th arm	HPC (delay-dependent) and ILn (delay-independent) impaired; ILn more strongly affected when external cues were minimised by lights out HPC impaired and had slower rate of improvement ILn showed virtually no improvement across trials

Table 3 (cont). Summary of Studies involving ILn / IML Lesions and the PTD model with Assessment of Performance in an array Memory Tasks over the past 20 years.

Year	Authors	Lesion/Size/Species/Type	Extra damage	Behavioural Tasks	Training	Delays	Deficits reported
1998	Burk & Mair	L-IML, ILn, MD L – rats; NMDA	L-IML: AD, AV, MD, PF, VL ILn: AD,AV, MD,LD, PF, Po, VL, VM, VA MD: CL, PC, VL, VM	Place DMTS, operant boxes Serial reversal learning	Pre-op, 75% correct	FR2 or 7 1, 3, 8, 13s	ILn lesion significantly impaired, L-IML slightly impaired and remained consistently impaired 8 months after surgery All able to perform reversal but ILn did make slightly more errors
1998	Savage, Castillo & Langlais	L-IML (CL, PC), ILn/midline (CL, PC, PF, AM, IAM, CM) L – rats: Ibotenic acid	L-IML: vAD, dAM. ILn/midline: MD, rhomboid, VL, Po, ATN, mMB (14%).	Successive object discrimination Water Maze Acoustic startle	Pre-op, 85% Post-op		No Yes, ILn/midline in both initial and repeated acquisitions No
1998	Zhang, Burk, Glode & Mair	Expt 1: Pyriform, ETR, L-IML , MD, PC-CL L – rats: NMDA Expt 2: ILn (PC, CL, CM), MD L – rats: NMDA	Similar lesion damage to other thalamic nuclei as reported below	Go/no-go DNMTS for odorants Olfactory discrimination learning	Pre-op	4, 6, 9, 13.5, 20.25s	Only pyriform and L-IML performed poorly; pyriform delay independent deficits. Only L-IML were impaired in learning the discrimination ILn lesion produced substantial and consistent deficits, MDn was smaller and more transient; no group was impaired on the olfactory discrimination learning task
1997	Savage, Sweet, Castillo & Langlais	L-IML, PC, CL PF / Po thalamic nuclei M/L – rats: RF	IML: AV, AM, CM, rhomboid, gelatinosus, MDv. mMB size significantly reduced in lesion groups (IML, 25%; Po, 6 %)***	T-maze (NMTP) Water Maze Passive avoidance Acoustic startle	Pre-op, 90% accuracy Post-op Post-op Post-op	5, 30, 60, 90 s	IML/ PC/CL impaired in re-acquisition; then impaired across all delays. PF/Po impaired on 60 and 90 s intervals IML/PC/CL impaired acquiring location of platform, and took twice as long in probe trial to reach the target No deficits Startle response significantly reduced in IML-lesion group across all blocks
1996	Young, Stevens, Converse & Mair	Expt 1: L-IML MDn Fornix L – rats: RF Expt 2: L-IML MW of PFC Dorsal Hippocampus Expt 3: L-IML, MW of PFC	L-IML: MDn PC, CL, MDpl, tracts to PFC MDn: PV, difficult to assume from the one plate, no detail in text. L-IML: same as expt 1 MW: FR2, Cg1-3 anterior to bregma HPC: dorsal only Similar to expt 2	DNMTS in operant boxes 8-arm Radial Maze DNMTS in operant boxes DMTS in operant boxes	Pre-op Post-op Pre-op Pre-op	1.8s – 8.8s 0.4s – 12.8s 1.5s – 6.0s	L-IML group more impaired than others, although all worse at greater delays L-IML, MDn and fornix lesions all produced deficits in acquisition of the radial maze task. Both L-IML and MW lesions produced comparable delay-independent deficits. HPC similar to controls. Both L-IML and MW lesions produced comparable deficits.
1996	Harrison & Mair	L-IML, MW of PFC, Rhinal Sulcus L – rats: RF	ML extends 0.9 – 1.1 mm, DV from habenula to CM, AP from 5.4 – 7.0 mm relative to IA, no other specific details	8 arm Radial Maze removal after 2nd, 4th, 6th reinforcements Serial reversal learning (operants)	Pre-op Post-op	1 min delay back in home cage	All groups worse after surgery but only L-IML lesion rats did not recover across 15 sessions All groups reach criterion on seven problems but L-IML lesion rats made more errors to criterion

Table 3 (cont). Summary of Studies involving ILn / IML Lesions and the PTD model with Assessment of Performance in an array Memory Tasks over the past 20 years.

Year	Authors	Lesion/Size/Species/Type	Extra damage	Behavioural Tasks	Training	Delays	Deficits reported
1995	Langlais & Savage	PTD – rats	IML-lesioned: PC, CL, PF, VL, VPM, VPL, AVVL, AVDM, MDv reticularis, MGN, LGN, mMB, CC thickness reduced, parietal/frontal cortex thinner IML spared: AVVL, MDv, CM, AM, Po	Passive avoidance Spontaneous activity Spontaneous alteration T-maze NMTP & DNMTP Reversal MTP & DMTP	Pre-op Post-op	 4s 30, 60, 90s	No group differences in post-treatment retention Similar across groups PTD-treated rats had significantly lower rate of alternation Significant differences in trials to criterion for PTD rats; all groups poorer with longer delays Significant difference in trials to criterion for PTD rats; and delay-dependent deficit at longer delays
1995	Mumby, Mana, Pinel, David & Banks	PTD – rats	Midline thalamus (CM, CL, PC, PF) and MD Po, but none in ATN	Simple object-discrimination (DNMS)	Pre-op & Post-op	4, 15, 30, 60, 120 s	Post-op trained PTD rats required significantly more trials to criterion than controls at 4s delay. Pre-op trained PTD rats showed delay-dependent deficits on trials to criterion for longer delays.
1994	Koger & Mair	L-IML, MW of PFC, RS L – rats: RF	Don't mention but indicate comparable to previous studies	Go/no-go DNMTS for odorants Olfactory discrimination	Pre-op	5, 10, 20, 40s	L-IML significantly impaired (delay independent), MW and RS were slightly impaired, transient effect All groups able to discriminate among odorants and perform go/no-go tasks
1992	Mair, Robinson, Koger, Fox & Zhang	Midline thalamus (ML - 0.1mm within midline), More lateral thalamus (ML- 0.9-1.2mm of midline; N= 8) L – rats: NMDA Anterior L-IML, Posterior L-IML Entire L-IML L – rats: RF	Don't mention but lesion ave. 0.69 +/- .03 mm in diameter… only mention much smaller than previous studies (Robinson & Mair, 1992; Mair & Lacourse, 1992) Mean diameter ave. 1.30 +/- 0.06 mm	DNMTS in operant boxes (water reward) Exploratory activity in open field	Pre-op to 85% correct criterion	3.0 secs 1, 3, 4.5, 6.8, 10, 15 secs	No deficits in either measure (latency or accuracy). Concluded the lesions were considerable smaller and also excitotoxic so spared fibres of passage. No differences in rearing responses or line crossing across groups Only entire L-IML impaired. No deficits if lesion restricted to either only the anterior or the posterior portion of L-IML.
1992	Mair & Lacourse	MT, L-IML, mMB, combined mMB / MT L – rats: RF FX – rats: RF	Spherical lesions of consistent size, ave 1.30 +/- 0.06 mm	DMNTS in operant boxes Exploratory activity in open field	Pre-op	4.5, 6, 7.5, 9, 12, 15, 18 s	Only L-IML lesions produced deficits on DNMTS and exploratory behaviour (less rearing in open field; comparable to rats with PTD model on same task); the other lesion groups did not differ from each other. Impaired smaller than L-IML and re-acquired task.
1992	Robinson & Mair	PTD treatment, PTD with MK-801 (NMDA antagonist) L - rats	PC, CM, MD, Pf, LGN, MGN, Re, medial MB	DNMTS in operant boxes 5/8 task Radial Maze	Pre-op Post-op	0 – 15 s No delay	PTD-treated rats impaired compared to controls and PTD-MK-801 treated rats PTD-treated rats impaired compared to controls and PTD-MK-801 treated rats but did eventually reach criterion.

Table 3 (cont). Summary of Studies involving ILn / IML Lesions and the PTD model with Assessment of Performance in an array Memory Tasks over the past 20 years.

Year	Authors	Lesion/Size/Species/Type	Extra damage	Behavioural Tasks	Training	Delays	Deficits reported
1992	Langlais, Mandel & Mair	PTD treatment L- rats	PC, CL, MD, Po, PF, LGN, MGN, VPM, VPL, mMB	Water Maze	Post-op		PTD-treated rats impaired compared to controls; PTD rats continued thigmotaxic strategies throughout the training sessions
				Water Maze - 5 weeks retention trials	Pre-op		PTD-treated rats demonstrated no memory loss of platform location acquired 2 wk prior to PTD injections
1991	Knoth & Mair	PTD treatment for 15- 16 days L- rats	Divided group into IML-lesion and IML-spared	Spatial NMTS in operant boxes	Pre-op	0 – 12 s	IML-lesion PTD-treated rats were impaired throughout, while the IML-spared PTD-treated rats gradually recovered across blocks of sessions
1991	Mair, Otto, Knoth, Rabchenuk & Langlais	PTD treatment for 18-21 days L - rats	Divided group into IML-lesion and IML-spared, medial mammillary bodies	Avoidance / escape learning in 4 arm radial maze, with NMTS condition	Post-op		IML-lesion PTD-treated rats impaired throughout, while IML-spared PTD-treated rats learnt NMTS but required more trials than controls All able to learn discrimination problems
1991	Mair, Knoth, Rabchenuk & Langlais	PTD treatment for 12-13 days L- rats	PC, CM, MD, Pf, LGN, MGN, Re, medial MB	Spatial, Olfactory and Auditory Serial reversal and MTS in operant boxes Auditory Go/No Go discrimination	Pre-op		IML-lesion PTD-treated rats impaired throughout session across all tasks, while others with IML-sparing were able to learn all tasks, although they were slower than controls.

For Abbreviations see Table 1 pg 54-56.

Typically, the deficits in memory performance following ILn lesions on the tasks mentioned above are delay-independent, which may suggest that other factors impeding the ability to recall information are disrupted rather than memory per se. That is, like the proposal related to the role of the MDn in memory, the ILn may play a role in other behavioural processes that then result in impairments of memory, due to links between the ILn, the ascending reticular formation and cortical areas. For example, in the human literature, Van der Werf and colleagues (2000, 2002, 2003) propose the ILn maintains a necessary state of arousal for cortical regions involved in ongoing memory processes, which suggests that damage to the ILn may affect arousal / attention / motivational factors and it is the disruption in these processes that then disrupts memory. This notion has been investigated in testing that assessed attentional processes following ILn lesions but while changes in latency to respond were reported these changes did not affect accuracy during a serial reaction time task (Burk & Mair, 2001). Burk and Mair concluded that the slower latencies caused by ILn lesions are consistent with impairment in motor intention affecting the ability to make a voluntary movement to an external stimulus, which they noted is observed with hypokinesia in patients and also in non-human primates with ILn lesions.

The ILn are also prominently connected with the striatum (see Chapter 6) and it has been suggested that lesions to the ILn may also be disrupting normal striatal functioning. Recently Burk and Mair (2001) investigated the effects of performance following lesions to the dorsal and ventral striatum in memory tasks that are sensitive to ILn lesions, for example delayed matching-to-sample tasks in operant boxes. They reported that the deficits in performance following lesions to the ventral striatum were comparable to the deficits in performance that they have demonstrated following lesions to the ILn. Interestingly the ventral striatum is associated with motor control (Groenewegen, 2003), although the conclusions drawn by Burk and Mair (2001) are somewhat confusing because it is documented that the ventral striatum is prominently connected with the more caudal aspects of the ILn and midline medial thalamic structures, as will be fully detailed in Chapter 6. However, the conclusions of Mair and colleagues align with the notion that damage to the ILn produces widespread deficits in memory processing, which are substantially different to memory deficits associated with just the hippocampal regions and the prefrontal cortex.

Therefore while it is evident that the ILn plays a role in memory, as yet no clear links can be discerned about a role for the ILn in memory processes because double dissociations have

not been reported. Further investigations are required with lesions to the ILn or IML that cause very little additional medial thalamic damage in order to fully determine a specific role for these structures in memory.

5.4.1 The Pyrithiamine-induced Thiamine Deficiency (PTD) Model

Within experimental animal models of medial thalamic amnesia the PTD model is used to mimic in rats the effects of thiamine deficiency associated with chronic alcoholism suffered by humans. There are some methodological issues involved with this model but it has proven successful at confirming the involvement of the medial thalamus in memory deficits associated with thiamine deficiency.

There are some conflicting reports of PTD-induced brain damage, which may in part be due to the duration of the thiamine deficiency treatment and magnitude of seizure induced symptoms before thiamine replacement intervention. Typically damage is centered on the intralaminar thalamic nuclei (Mair et al, 1994) and internal medullary lamina pathway of the thalamus (Mumby, Cameli, & Glenn, 1999). Additionally others have reported that the anterior thalamic nuclei (Langlais & Savage, 1995) and medial mammillary bodies (Mair et al, 1991) are also significantly affected in animals exposed to research involving the PTD model. It has been reported that typically the longer the exposure to the course of thiamine deficiency the more extensive the damage. For example it has been noted that in animals reversed at later and more advanced symptomatic stages of thiamine deficiency, degenerating axons are found in cortical regions and the hippocampus and there is more extensive neuronal loss and gliosis within the mammillary body and medial thalamus (Langlais & Zhang, 1997). Additionally, the extent of seizure-like symptoms appears to correlate with the amount of damage to the IML, that is to say, whether it is fully lesioned or subsequently spared (Savage et al, 1999). Interestingly, these changes in brain damage are also apparent in humans from neuropathological reports of differences in brain atrophy amongst non-amnesic alcoholics, patients with Wernicke's encephalopathy (thiamine deficiency), and those with the amnesic Korsakoff's syndrome (see Harding et al, 2000; Kril & Halliday, 1999).

Despite these methodological issues, the PTD model has indicated a role for the medial thalamic nuclei in memory processes stemming from thiamine deficiency. Mair and colleagues (1992) have concluded that lesions must extend throughout the AP extent of the IML site to produce impairments in DNMTS performance comparable to those of the PTD model.

Accordingly, other researchers have suggested that limited damage to the IML pathways or to thalamic nuclei (PC / CL) from the IML lesions can not account for deficits observed in PTD rats. Instead, they conclude the PTD-induced amnesic deficits occur either from damage outside IML or from combined IML and other area damage but not necessarily MDn (Mumby et al, 1999; Savage et al, 1998).

5.5 Current Perspectives

As indicated from the above surveys of the individual contribution of the medial thalamic nuclei to specific forms of memory, some conclusions have been drawn but much debate remains about the neural basis of profound amnesia that can occur following damage to the medial thalamus.

It is clear from the evidence thus far that the AT plays a critical role in spatial memory and that it is interconnected in a circuit that also contributes to spatial information processing (Aggleton & Brown, 1999) but also still a degree of disagreement whether MD or ILn influence spatial memory. In contrast, it is not as clear what specific forms of memory the MDn and ILn are involved in. Moreover the memory impairments associated with damage to both the MDn and the ILn have been attributed to their significant connections with the PFC and in the case of the ILn also the ascending reticular formation and striatum. As previously indicated it is proposed that damage to the MDn and ILn disrupt normal functioning in their associated PFC structures and this disruption is primarily impairing higher cognitive processes like attention, which leads to the secondary deficits, for example memory impairments. This proposal of MDn and ILn involvement in memory implies that they may not contribute a functional role to specific forms of memory at all.

Therefore further investigations are needed into the memory functions of the medial thalamus. This further investigation will begin with an extensive re-assessment of the prominent neural connections of the medial thalamus (Chapter 6), in order to determine to what extent the ILn and MDn also form interconnected circuits, as identified for the AT, with other brain structures that have a role in processing specific forms of memory.

Chapter 6

Connections of the Limbic, Midline and 'Non-specific' Thalamic Nuclei

The following chapter examines in greater detail the prominent neural connections of the medial thalamus between other structures located in the midbrain / brainstem, basal ganglia, amygdala thalamus, hippocampal regions and frontal cortex. Furthermore it assesses the neural connections of other adjacent thalamic nuclei before reviewing the types of behavioural and memory deficits associated with functionally connected regions of the medial thalamus.

6.1 Introduction

This review of the anatomical connections within the brain centers on the medial thalamus and it will provide a basis from which to suggest diversity of memory function in particular is associated with different aggregates of medial thalamic nuclei. This approach involving assessment of anatomical connections has been adopted by other researchers, but these assessment usually focus on only one component of medial thalamic nuclei, for example the neural connections of the AT nuclei have been documented by Aggleton and colleagues (Aggleton and Sahgal, 1993; Aggleton and Brown, 1999). The neural connections of the MDn have been investigated by Groenewegen (1988) and Gaffan and colleagues (2002; Easton et al, 2000), while Mair and colleagues (1994; Mair et al, 1998) and Van der Werf et al (2002) have investigated the neural connections of the ILn and midline thalamic nuclei.

It is now recognised that individual structures within the brain do not work alone in carrying out the brain's functions, rather each individual structure or nuclei works in concert with many other interconnected structures to form circuits that are involved in the brain's functioning. Generally then, it is well known that nuclei of the medial thalamus form critical connections with a variety of other cortical and subcortical brain structures. The anterior nuclei has interconnections with retrohippocampal regions, retrosplenial and cingulate cortices and the mammillary bodies; the intralaminar nuclei have interconnections with the basal ganglia,

frontal cortex and midbrain / brainstem; and the mediodorsal nuclei have interconnections with the amygdala, basal ganglia, and prefrontal cortex.

It remains less well understood whether the traditional groupings of the thalamic nuclei, i.e. anterior, intralaminar, mediodorsal and midline groupings are working together or separately as individual nuclei in independent circuits involved in processing information. Recently, for example, a connections review (van der Werf et al, 2002) focusing on the intralaminar and midline nuclei suggested these two groupings of nuclei should be re-clustered into four separate groupings based on their significant interconnections with other structures of the brain.

Upon re-assessing the prominent connections that link the medial and the non-specific thalamus with other significant brain structures it has became apparent during this thesis that there are some further commonalities amongst the nuclei with regard to their afferent and efferent connections. These commonalities suggest that at least three aggregates exist incorporating related thalamic nuclei, one conventional and two non-conventional groupings, with connections to other neural structures that together form segregated neural circuits (Aggleton & Brown, 1999; Eichenbaum & Cohen, 2001; Kesner, 1998; McDonald & White, 2002). These independent neural circuits have been shown to actively participate in processing a variety of functions including various behavioural and motor outputs, and learning and memory processes (see Chapters 3 and 4).

Therefore the following review assesses the significant neural connections of individual nuclei within the medial thalamus, based on existing tracing studies that have focused on connections in the rat brain. There is also some mention of relevant connections using other mammals (cats), non-human primates and humans. This review establishes the background information for the hypotheses concerning the non-traditional groupings of the medial thalamic nuclei. The research literature covered in this review mainly includes publications within the past two decades, with only infrequent reference to older works because advances in tracing techniques have made the recent studies more accurate. For example, more recent studies using anterograde transport techniques such as biotinylated dextran amine, *Phaseolus vulgaris* leucoagglutinin (PHA-L) or biocytin are able to provide more detailed information about density levels and distributions of the pathways than the older horseradish peroxidase or radioactive amino acid techniques (Pitkanen, 2000).

This neuroanatomical review of the medial thalamus has focused on other neural structures thought to be involved in some ways with learning and memory or motivational /

attentional processing, namely the hippocampal and retro-hippocampal regions, the mammillary bodies, the amygdala, the prefrontal cortex (both medial and lateral regions), the striatal region, the pallidal region and the midbrain / brainstem. This approach was taken in order to focus on the circuitry widely regarded to be involved in memory processes so that the current proposals that position the medial thalamic nuclei within these neural circuits may be readily illustrated, as opposed to simply listing the connections of the thalamic nuclei. At the conclusion of this chapter, it will be argued that the various medial thalamic nuclei form functional components of these widely regarded multiple memory systems and the types of memory deficits associated with disruptions to these neural circuits will be discussed.

The review begins with an assessment of neural connections of the medial thalamic nuclei and the limbic system structures (6.2), followed by frontal cortex structures (6.3), the basal ganglia complex structures (6.4), and midbrain / brainstem structures (6.5). Within each section summary tables of the efferent and afferent connections have also been compiled identifying the interconnections of medial thalamic, adjacent aggregations and other neural structures. Furthermore each section is divided into subsections that focus on the relevant efferents from individual thalamic nuclei to the above structures are covered first, followed by an overview of afferents to the individual thalamic nuclei. At the conclusion of each section, there is an overview of intra- and inter-system connections.

6.2 Limbic System Connections

The limbic system structures include the hippocampal formation, which consists of the dentate gyrus, the hippocampus proper (CA3, CA2, and CA1), the subicular complex (subiculum, pre-, and para-subiculum) and the entorhinal cortex (lateral and medial subdivisions; Amaral & Witter, 1995). Other structures of the limbic system include the adjacent cortical areas of the perirhinal and postrhinal cortices, as well as the posterior cingulate cortex and retrosplenial cortex. Sub-cortical structures include the basal forebrain (septum, vertical and horizontal limbs of diagonal band of Broca, and nucleus basalis of Meynert); mammillary bodies; and amygdala. The connections of the anterior cingulate cortex will be covered in the section 6.3 Frontal System Connections.

An overview of the significant neural connections and density ratings of the medial thalamus and limbic system structures are presented in Table 4 (on p. 77-78) with further details of the interconnections described below. Within the tables, the interconnections have been graded using a number from 1 to 3, in order to indicate the intensity of the connections,

whereby 1 = a light connection, 2 = a moderate connection, and 3 = a heavy connection, while -- = no connection and * = connection but the intensity could not be determined from the descriptions in the literature.

Table 4a. Limbic System Connections showing the Afferents of the Medial Thalamic Nuclei

	AVd	AVv	AMdl	AMvm	AD	LD	CL	PC	MDl	MDpl	MDm rostral	MDm caudal	MDc	CeM rostral	CeM caudal	IMD	PV	PT	IAM	Re	Rdg (Area 29d)	Rgb (Area 29c)	Rga (Area 29a/b)	DG	CA1-CA3	SUB	PRE-S	PARA-S	ENT	PRh	LM	MM	BL	SPFC/AHA A	CE/ MD A	Septal M vs L
AVd	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	3	2^{I}	--	--	1	2d 3v	2	2m	1	--	--	--	--	--	--
AVv	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	3	2^{I}	--	--	1	2d	2	1^{IV-VI}	--	--	--	--	--	--
AMdl	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	3 cd	1	1	--	--	R3	r2v	--	$3I^{IV-VI}$	2^{V}	--	--	--	--	--
AMvm	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	3 rd	1	1	--	--	R3	--	--	*	2	--	--	1	--	--	--
AD	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	3	$3^{I,III,IV}$	--	--	I	3d	2^{IV-VI}	2^{V-VI}	1	--	--	--	--	--
LD	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	V $3^{I,III-I}$	V I^{I}	RD 1^{I}	--	--	--	3d	3	1 m IV-VI	--	--	--	--	--	--	--
CL	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	1d	--	--	--	--	--	--	--	--	--
PC	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	I	1d	--	--	I	--	--	--	--	--	--
MDl	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
MDpl	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
MDm rostral	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	2Bl	*	*	--
MDm caudal	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	2Bl	*	*	--
MDc	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
CeM rostral	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	2v L	1	--	--	2 Bl	--	--	--
CeM caudal	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	1 v	1	--	--	2	1	1	--
IMD	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	$3\,I^{V}$	I v L,V	--	--	2La	I	1	--
PV	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	1	1	3v	--	--	2 m	2	--	--	3bl	2	1Ce	--
PT	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	1	1	1 v	--	--	2 I V,VI	1	--	--	1d BL	--	--	--
IAM	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	2	--	--	--	--	--	1	1	$3\,I^{IV}$	2^{V}	--	--	I	1	1	--
Re	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	1	1	1	--	3	3	*	*	3	3	--	--	*	*	*	--

Table 4b. Limbic System Connection showing the Efferents to the Medial Thalamic Nuclei

	AVd	AVv	AMdl	AMvm	AD	LD	CL	PC	MDl	MDpl	MDm rtrl	MDm cdl	MDc	CeM rtrl	CeM cdl	IMD	PV	PT	IAM	Re	Rdg	Rgb	Rga	DG	CA1-CA3	SUB	PRE-S	PARA-S	ENT	PRh	LM	MM	BL A	SPFC/AHA A	CE/ MD A	Septal L vs M
Rdg	3	3	c3 rost	r1 caud	1	r3m c3dl	--	--	--	--	--	--	--	--	--	--	--	--	--	1	3	1	3	--	--	--	3d 1v	1	1 cm	--	--	--	--	--	--	2
Rgb	c3rd	r3cv	--	--	2	3v m	*	--	--	--	--	--	--	--	--	--	--	--	--	--	*	X	3 l	--	--	--	1d 3v	*	3m c	*	--	--	--	--	--	*
Rga	3	2	1	1	1	3 d	--	--	--	--	--	--	--	--	--	--	--	--	1	--	3 l-III	3c I–III 2r II-III	3 contra	--	--	--	1d 3v	1	1mc	--	--	?	?	--	--	*
DG	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	3	--	--	--	--	--	--	--	--	--	--	--
CA1-CA3	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	*	*	1	3	3	3	*	*	3m 2l	2	--	--	2	1	--	3l
SUB	--	--	--	--	--	--	--	--	--	--	*	--	--	--	--	--	--	--	--	*	*	D3	V3 I-III	--	--	X	3d 3v	3 III	3m 2l	3	1	D3	3	1	1	3l 2m
PRE-S	d3 v1	--	v2	--	d3 v1	d3 v3	--	--	--	--	--	--	--	--	--	--	*	--	*	*	1d	3	3	1	1	1	3d	3 III	3m I III	--	3	3	--	--	--	--
PARA-S	1	--	--	--	3	--	--	--	--	--	--	--	--	--	--	--	--	--	--	*	--	--	--	1	3	2	3d	X	3m 1l	--	3	3	--	--	--	--
ENT	M 3 rd	--	--	--	--	x 3d	--	--	--	--	L2	L2	--	--	--	--	*	--	--	*	*	*	--	3	3	3	2d 1v	1	X	3	MI	--	3	3	*	3l 1m
Prh	--	--	--	--	--	--	--	--	--	--	*	*	--	--	--	--	--	--	--	--	*	*	--	M*	*	3	2d ?v	?	3 III,III	X	--	--	3	*	*	--
LM	--	--	--	--	3	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--
MM	pb 3 pp 3 l	l 3 pl 3	pm 3d	pl 3dm	pb 3	--	--	--	--	--	--	--	--	--	--	--	--	--	pm 3d	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--
BL A	--	--	--	--	--	--	--	--	--	--	3	3	--	--	--	--	*	--	*	--	--	--	--	2	2	2	1v	3	3	3	--	--	X	*	*	*
SPFC/AHA A	--	--	--	--	--	--	--	--	--	--	*	*	--	*	*	--	--	*	*	*	--	--	--	*	*	*	--	--	--	--	--	--	--	X	*	*
CE/ MD A	--	--	--	--	--	--	--	C*	--	--	*	*	--	*	*	*	*	--	--	--	--	--	--	1v	1v	1	--	cm 3	m3 I-III	3 I,II	--	--	*	*	X	*
Septal L vs. M	--	--	--	--	--	--	--	--	1	1	3	3	3	--	--	--	1	2	--	--	--	--	--	m3	m3	m2	2d 3v	2	m3m	--	3l	3m	*	*	*	3

6.2.1 Thalamic Afferents of the Limbic System

The Hippocampal Formation – Hippocampus Proper (CA1-CA3) and Dentate Gyrus

The laminar organisation in the hippocampus is relatively simpler than other regions of the cortex and has thus permitted greater clarification of the anatomical organisation of this structure (Swanson, 1987).

Within the medial thalamus, some of the midline thalamic nuclei are the only structures that project directly to the hippocampus and dentate gyrus. The midline nucleus reuniens (Re) projects prominently to the field CA1, via the internal capsule and cingulum bundle rather than through the fimbria/fornix. The Re projection to CA1 is topographically arranged so that the more rostral Re projects to the more septal portions of CA1, whereas the more ventral Re projects more temporally in CA1 (Amaral & Witter, 1995). The parataenial (PT), and anterior part of the paraventricular (PV) nuclei send weak projections to DG and CA3 (Berendse & Groenewegen, 1991; Swanson, 1987).

The Hippocampal Formation - Subicular Complex

The subicular complex consists of the pre-, and para-subiculum and the subiculum proper. It is sometimes referred to as the retro-hippocampal cortex and consists of several cortical fields located between CA1 and the entorhinal cortex ventrally, and CA1 and the retrosplenial cortex dorsally. In the rat, it is generally accepted that the subiculum is the major output structure of the hippocampus; it is where most of the fornix fibres originate (Amaral & Witter, 1995). However, the roles of the pre- and para-subiculum remain somewhat uncertain. The pre-subiculum has a dorsal and ventral subdivision and sometimes the dorsal pre-subiculum is labeled the post-subiculum (Amaral & Witter, 1995). It is proposed, due to their significant connections, that the pre- and para-subiculum regions are major input structures of the hippocampus, in a similar manner as the entorhinal cortex. For example, the pre-subiculum receives a dense projection from the retrosplenial cortex (Wyss & van Groen, 1992), and as will be detailed below the anterior thalamic nuclei projects to both the retrosplenial cortex and pre- and para-subiculum. Therefore it appears that the pre- and para-subiculum form the major route through which the thalamus influences the hippocampal formation (Amaral & Witter, 1995).

As Table 4 shows, the anterior thalamic (AT) nuclei project extensively to the subicular complex. The projections of the anteroventral (AV) nucleus of the AT to the subicular complex

are organised in a complex topographical manner. The AV project to the deep pyramidal cell layer of the subiculum, and the pre- and para-subiculum (Shibata, 1993). The rostral aspects of the dorsal AV project heavily to terminals in layers I, III of the ventral pre-subiculum. At the mid-rostrocaudal level, the lateral part projects to layers I and III, and the dorsal part projects to layer I, IV-VI of the ventral subiculum, whereas the ventral AV projects to I and III and the medial part projects to I and IV-VI in the dorsal pre-subiculum (Shibata, 1993). The rostral part of the anteromedial (AM) nucleus of the AT sends dense projections to the subiculum, terminating within the deep part of the pyramidal cell layer of the ventral tip. The rostral AM has less dense terminal fields in the pre-subiculum; these are predominantly in layer V with a few axons terminating in layer I. The caudal AM sends sparse projections that terminate in the ventral tip of the pre-subiculum (van Groen et al, 1999). The anterodorsal (AD) nucleus of the AT project to pre-and para-subiculum (Shibata, 1993; van Groen & Wyss, 1992). The AD projects mainly to the deep layers of the pre-subiculum and layers I, IV-VI of the para-subiculum. Van Groen et al (1995) confirmed these findings and proposed that both AD and AV project densely to the pre- and para-subiculum and lightly to the subiculum. They report that the major connections of the medial thalamus to dorsal pre-subiculum (post-subiculum) originate in AD, with lesser connections from AV. The AD projections terminate in layers I-III and V, whereas the AV projects to layers I and V (van Groen & Wyss, 1995). In conclusion all of these inputs from the AT into pre-subiculum appear to be in a position to influence the projections from Layers II and III of the pre-subiculum to the medial entorhinal cortex, thus 'constituting the final link in the feedback loop' (Swanson, 1987).

The laterodorsal (LD) thalamic nucleus also has significant projections to the subicular complex (van Groen & Wyss, 1992). In the pre- and para-subiculum, the rostrodorsal LD has projections to layers IV-VI. The caudal parts of the dorsal LD project primarily to dorsal pre-subiculum in layers I and III / IV and extend into the superficial layer V (van Groen & Wyss, 1992; Shibata, 1993).

The midline nuclei also project to the subicular complex. The anterior part of the PV, PT and Re all project to the subiculum, terminating mainly in the molecular layer of the ventral subiculum, although some terminals from the PV terminate in the pyramidal layer (Amaral & Witter, 1995; Berendse & Groenewegen, 1991). The projections from the Re to the subiculum run in a topographical manner, with the dorsal Re projecting to dorsal subiculum and ventral Re projecting to ventral subiculum. The Re also projects to Layer I of the para-subiculum

(Swanson, 1987). Another study using PHA-L injection into the Re also reported projections to the molecular layer of the subiculum, pre- and para-subiculum (Zheng, 1994).

The Hippocampal Formation - The Entorhinal Cortex (ENT)

The entorhinal cortex makes up the final part of the retrohippocampal region and it is located medial and ventral to the rhinal sulcus. It comprises two major regions: a medial area and a lateral area, and is subdivided into six layers: I-III are the superficial layers and represent the major input to the hippocampal formation, including the dentate gyrus, hippocampus and subiculum, while IV-VI are the deeper layers, which receive processed information from other hippocampal fields. The perforant pathway, a major nerve fibre bundle of the hippocampus, originates within layers II and III of the superficial layers of ENT and terminates in all subdivisions of the hippocampal formation (Amaral & Witter, 1995).

The major thalamic inputs to the entorhinal cortex are from the ILn and midline nuclei, including the Re and CeM, with only minor inputs reported from the rhomboid, PV, PT and intermediodorsal (IMD) thalamic nuclei (Amaral & Witter et al, 1995; Berendse & Groenewegen, 1991; Witter et al, 1989). Fibres from Re terminate densely in the deep part of layer I and III, and only lightly in layer II of the entire ENT (Swanson, 1987; Witter et al, 1989). The projections from Re to the ENT arise from a separate population of neurons to those that project to CA1 and subiculum (Dolleman-van der Weel & Witter, 1992, cited in Amaral & Witter, 1995). The PVA projects to the most medial ENT and the CeM projects most strongly to the lateral part of the lateral ENT with the rostral CeM sending moderate fibres pathways to terminate in layer I of ENT (Witter et al, 1989). The PT projects to lateral ENT with terminals in layers V and VI. There are dense projections from the IMD nucleus terminating throughout the lateral part of the ENT in layer V, but not the medial ENT (Berendse & Groenewegen, 1991).

Earlier studies reported no projections from the AT terminate in the ENT, but recent studies have indicated some inputs from the AT sub-nuclei exist (Shibata, 1993). The more rostral and dorsal parts of the AV projects moderately to the medial ENT and a few fibres to the lateral ENT, terminating in layers V and VI. The AM projects to layers IV-VI of the lateral part of the lateral ENT, layer IV of the caudal part of the medial ENT, and caudomedial part of the lateral ENT. The interanteromedial (IAM), which is located between the left and right AM and spreads across the midline of the thalamus, projects to layer IV of the caudolateral part of the lateral ENT. The AD projects to layers V and VI of the ENT (Shibata, 1993; van Groen &

Wyss, 1995). A small number of rostrodorsal LD axons terminate in the deep layers (IV-VI) of the medial ENT (van Groen & Wyss, 1992).

According to Amaral and Witter (1995), there are no projections from the MDn to the entorhinal cortex. Additionally Groenewegen (1988) reports no MDn input to the ENT.

The Perirhinal (Prh) and Postrhinal (POs) Cortices

The Prh cortex is situated along the fundus and lateral bank of the rhinal sulcus. It is a major component of the parahippocampal region in rats, monkeys and humans (also referred to as the parahippocampal gyrus, although this label is mainly used for primates and humans; see Burwell et al, 1995). Brodmann labeled the two areas that constitute the Prh, areas 35 and 36, (this latter area, 36 has previously been referred to as the ectorhinal cortex). Recently, a new terminology for these cortical regions was introduced whereby Prh refers to the rostral portion of the region and Postrhinal (POs) cortex refers to the caudal portion of the region (Burwell, Witter & Amaral, 1995).

As Table 4 indicates only selective regions of the medial thalamus project to the Prh and POs. Witter et al (1989) reported projections from the Re and CeM to the Prh. In addition, a few fibres from the PT, caudal part of PC and CL, and a moderate number from the PV terminate in the Prh. There are also projections from the IMD terminating in layers I and V of the ventral Prh (Berendse & Groenewegen, 1991). Within the AT, the medial AM, as well as the IAM both project to layer V of the Prh (Shibata, 1993; van Groen et al, 1999).

There are no connections reported of MDn innervating the Prh or POS (Burwell et al, 1995; Witter et al, 1989).

The Posterior (Retrosplenial) Cingulate Cortex

The essential cingulate cortical areas comprise of three relatively equal sized areas of cortex in the rat, these three areas are present in all mammals. The anterior cingulate cortex is agranular because it lacks a layer IV (and its connections will be summaries in section 7.3). The other two areas are in the posterior cingulate also named the retrosplenial cortex. These two areas are either dysgranular with only a thin layer of IV or granular with densely granular layers II-IV (Vogt, 1993). The retrosplenial cortex has also been labelled Brodmann's area 29. Areas 29a and b correspond to the retrosplenial granular a (Rga) and 29c corresponding to granular b (Rgb) cortical areas (van Groen et al, 1993). Area 29d, located in dorsal retrosplenial cortex,

corresponds to the retrosplenial dysgranular cortex (Rdg; van Groen & Wyss, 1992; van Groen et al, 1999).

The interconnections of the retrosplenial cortex and anterior thalamic nuclei have been examined in a number of recent neuroanatomical tracing studies and they are denser and more complex than previously reported (Shibata, 1993, 1998; van Groen & Wyss, 1995; van Groen et al, 1999). The connections are reciprocal between the cingulate cortices and the anterior nuclei (running via the cingulum bundle and internal capsule) but these reciprocal connections in most cases do not match locations. The AV has more caudal projections than the AM; it projects predominantly to the retrosplenial cortex, while the AM projects mainly to the dorsal anterior cingulate and also to the retrosplenial cortices (Ahmed et al, 1995; Bentivoglio, et al, 1993; Neafsey et al, 1993; van Groen et al., 1993, 1999). In addition, it is the more lateral parts of AM that project to the retrosplenial and cingulate cortices (Conde et al, 1995). The AM project to all areas of the retrosplenial cortex (van Groen et al, 1999). The rostral AM project to layers I and IV-VI of Rdg, and layers I and V of the caudal part of Rga and Rgb. In contrast, the caudal AM project to layers I and V of the rostral part of Rga and Rgb. The IAM only projects to layers I, V/VI of Rdg. Both AV and AD project to the full extent of the Rga and Rgb, in a topographic manner. Neurons in caudal parts of both AD and AV, project to rostral retrosplenial cortex, while neurons in rostral AD and AV project to caudal retrosplenial cortex. The AV project densely to layer I (Rgb) and lightly to layer IV (Rga) of the granular area, and the AD projects with equal density to layers I, III and IV (Rga and Rgb) of the granular area (Shibata, 1993; van Groen & Wyss, 1990; 1995).

The LD and Re also project to retrosplenial cortex. The LD projection to Rdg is dense with terminal fields in layer I and III-IV, while it only projects to layer I of the Rga and Rgb. There are only a few neurons from Re projecting to Rdg and to the Rga and Rgb of retrosplenial cortex (van Groen & Wyss, 1990; 1992).

In summary, the AT projections to retrosplenial cortex are quite distinct. AD primarily innervates areas Rga and Rgb; AV primarily innervates area Rgb, while AM projects primarily to area Rdg. The LD also projects predominantly to area Rdg and only sparsely to Rga and Rgb.

The Mammillary bodies (MB)

The MB are located in the hypothalamus at the very base of the brain, and they consist of medial and lateral mammillary nuclei. There are also a number of other nuclei which form the mammillary complex, including the supramammillary and tuberomammillary nuclei, but description of the entire mammillary complex interconnections is beyond the scope of this thesis. The intimate relationships of the mammillary bodies with the hippocampus and with the AT are well known. Papez (1937, cited in Swanson, 1987) suggested these pathways form a closed circuit that plays a critical role in emotional expression. Although this proposal of the functional role of the Papez circuit has since been seriously questioned, the circuit remains critical to cognitive processing carried out by the brain (Aggleton & Brown, 1999; Swanson, 1987). Although the MB project massively to the AT (as will be discussed in the section below titled Limbic Systems Efferents), but this interaction is not reciprocal (Shibata, 1992).

They are no other known connections between the MB and the rest of the medial thalamic nuclei. For a more detailed overview of other limbic system and brainstem inputs to the MB see the final summary at the end of section 6.2.

The Amygdaloid Complex

The amygdaloid complex consists of a heterogeneous group of 13 cyto-architectonically and connectionally distinct nuclear and cortical structures; it is located at the anterior, medial and ventral edges of the temporal lobe region. The descriptions and connections of all of these nuclei and structures are beyond the scope of this thesis (for an excellent overview, see Aggleton, J.P. (Ed), The Amygdala, 2nd ed (2000)). Some grouping of the amygdala nuclei is possible, although the groupings do not imply that the nuclei are functional similar (Pitkanen, 2000). The deep 'basolateral' nuclei include the lateral nucleus, basal nucleus, and accessory basal nucleus, which have significant interconnections with the cortex, hypothalamus and basal forebrain (Krettek & Price, 1977; McDonald, 1998). The superficial-cortex like (olfactory) nuclei includes the anterior cortical nucleus, amygdalohippocampal area, bed nucleus of the accessory olfactory tract, nucleus of the lateral olfactory tract, periamygdaloid cortex and posterior cortical nucleus; this grouping has significant connections with the olfactory bulb, cerebral cortex and hypothalamus (Krettek & Price, 1977). The central nucleus has strong interconnections with the brainstem, and the medial nucleus interconnects with the olfactory bulb, hypothalamus and pre-optic area (cited in Reardon & Mitrofanis, 2000; McDonald, 1998; Pitkanen, 2002; Price et al, 1987). These groupings are relatively similar across species of rat, cat, monkey, and human (cited in Pitkanen, 2000).

The medial thalamic nuclei that project to the amygdala are the mediodorsal (MDn) and midline structures as well as a specific part of the AM nucleus. The medial AM in the most caudal parts sends a few axons to form small terminal fields in lateral and basolateral amygdala (van Groen et al, 1999). The medial segment of MDn projects to basal and anterior cortical nuclei of the amygdala. The IMD projects strongly to amygdala; their fibres are directed at the central nucleus and the rostral part of the basolateral nucleus, whereas the caudal part of the latter nucleus is avoided (Groenewegen et al, 1990; 1991). The rostral CeM projects to dorsal region of basolateral nucleus, while the caudal CeM has more diffuse projections to basal, central, medial, anterior cortical, nucleus of lateral olfactory tract nuclei (Groenewegen et al, 1990; 1991). The PV has diffuse projections to the amygdala. There are dense PV fibres terminating most prominently in the caudal part of the basolateral nucleus, with moderate fibre terminals in the lateral, basal, accessory basal, central, anterior cortical nuclei and lighter terminals in the medial nucleus and amygdalohippocampal area (Pitkanen, 2000; van der Werf et al, 2002). Other midline nuclei project to the amygdala, including the PT, IAM, and Re. The PT project to lateral, basal, accessory basal, central and medial nuclei and the anterior cortical area while the IAM project to the lateral, basal and central nuclei and the nucleus of the lateral olfactory tract. The Re project to the basal, central and medial nuclei and the anterior cortical area (Pitkanen, 2000).

The Basal Forebrain

The septal region can be divided into four main components based on its significant connections, a lateral division consisting of the lateral septal nucleus; a medial division consisting of the medial septal nucleus and nucleus of diagonal band of Broca; a posterior division consisting of septofimbrial and triangular nuclei; and a ventral division consisting of the bed nuclei of stria terminalis. Broadly the first three of these areas are mainly associated with the hippocampal formation, while the ventral division is associated with the amygdala, especially central nucleus of amygdala (Swanson, Kohler & Bjorklund, 1987).

The table of limbic system connections uses the terms lateral septal region and medial septal region. The nomenclature is identical to that used by Witter and colleagues (Witter et al, 1989). The lateral group is ventrally continuous with the nucleus of the diagonal band and the medial group consists of the medial septal nucleus and the nucleus of the diagonal band.

6.2.2 Limbic system efferents

The Hippocampal Formation – Hippocampus Proper (CA1-CA3) and Dentate Gyrus

The dentate gyrus has no external projections other than those to the mossy fibres of the CA3 field (Amaral & Witter, 1995), whereas the hippocampal fields CA1-CA3 project to the subiculum, the septum, and the entorhinal, perirhinal, retrosplenial / cingulate cortices and the medial prefrontal cortical areas. Thus it is via these latter regions that the medial thalamus is influenced by hippocampal processing and vice versa (Amaral & Witter, 1995).

The Hippocampal Formation – The Subicular Complex

Van Groen, Wyss and colleagues investigated the subicular complex efferents to the rat medial thalamic nuclei. Although subicular projections to the AT have been described in the literature (Swanson & Cowan, 1977), more recent retrograde tracing studies have indicated that these projections arise mainly from the adjacent pre-subiculum (van Groen & Wyss, 1990a-c). The projections reach the medial thalamus via the fornix and via the internal capsule (Meibach & Siegel, 1977; Oda, 1997).

Layer VI of the pre-subiculum projects ipsi-laterally to the rostral AM and dorsal part of the LD; there are also more dense bilateral terminal fields in the dorsal and rostral parts of the AV. Contralaterally, a few terminal fields are located in the AD (Oda, 1997; van Groen & Wyss, 1990; 1992). The dorsal pre-subiculum (post-subiculum) projects more densely to AD and LD nuclei and lightly to the rostrodorsal AV nucleus (van Groen & Wyss, 1990; 1992).

The para-subiculum (layers IV-VI) mainly projects to the rostral parts of the AD whereas there are only very few terminal fields present in the AV. There is no projection from the para-subiculum to the LD (van Groen & Wyss, 1990; 1992).

There are also subicular fibres that project to the midline nuclei, including the IAM, PV, and Re (van der Werf et al, 2002) and the most medial segment of the MDn receives a projection from the subiculum (Groenewegen, 1988).

The Hippocampal Formation – The Entorhinal Cortex (ENT)

There are projections from ENT to selective nuclei of the medial thalamus (Shibata, 1996). There exists a direct projection from layers V and VI of the ENT to the AV and LD thalamic nuclei that runs via the internal capsule. The rostral part of the medial ENT projects to the AV, while the caudal part projects to the LD. These ENT connections reciprocate the afferent

connections. There are no terminals fields in AM or AD, despite their projections to the ENT (see The Entorhinal Cortex inputs above; Shibata, 1996). The lateral ENT projects to the most medial segment of the MDn (Groenewegen, 1988) and Van der Werf et al (2002) noted that there is a projection from ENT to the midline PV nucleus. In the monkey, Aggleton et al (1986) reported a projection from the ENT to the LD nucleus and Russchen et al (1987) reported a projection from ENT to the medial magnocellular segment of MDn.

The Perirhinal (Prh) and Postrhinal (POr) Cortices

The neuroanatomical tracing studies in rats are not very clear about Prh and POs projections to the medial thalamus. In monkeys, Aggleton et al (1986) and Russchen et al (1987) provide evidence that the medial magnocellular part of the MDn receives fibres from the Prh. In the rat, only the rostral portion of area 35 of the Prh projects to the MDn (Burwell et al, 1995).

The Posterior (Retrosplenial) Cingulate Cortex

Shibata (1998) conducted a comprehensive study of projections from the retrosplenial cortex to the AT in the rat. Some of the tracing evidence is in agreement with previous earlier studies (van Groen & Wyss, 1990; 1992; van Groen et al, 1993), although Shibata has been able to provide more precise detail of the interactions between the retrosplenial cortex and AT with more advanced biotinylated dextran amine tracing techniques. Rga (areas 29a and b) project predominantly ipsilaterally to the rostral and rostrodorsal magnocellular AV, with area 29a producing more rostral and more dorsal projection fields in the AV, than area 29b. Areas 29a and b also produced sparse preferential projection fields in rostral AD. The projections from Rgb terminate mainly in the AV and LD with only a few projections terminating in the AD, Rt, and Re. There is a topographic organisation between the rostral Rgb and rostral AD, and caudal Rgb projecting to caudal AD. In addition, Rgb has now been documented to terminate in the more ventromedial AV, amongst both magnocellular and parvicellular divisions (Shibata, 1998). Van Groen and Wyss (1992) indicated that Rdg only projects to the AM, however Shibata (1998) has also demonstrated the existence of massive projections from area Rdg to AV and sparser ones to AD. The projections for Rdg terminate in the dorsal and dorsomedial AM, adapting a rostrocaudal dimension, whereby the rostrocaudal Rdg corresponds to the caudorostral AM and the rostral Rdg projections to the caudal AM are relatively weak. Instead the caudal AM appears to receive massive projections from area 18 (visual cortex), which adjoins Rdg. The IAM does not receive any projections from Rdg (Shibata, 1998). Projections

from Rdg to AV terminate in the dorsolateral part. In a similar manner as the AM projections from Rdg, these AV projections are also organised on a rostrocaudal dimension: the rostral Rdg projects bilaterally to caudal AV, and caudal Rdg projects ipsilaterally to rostral AV.

The Mammillary bodies (MB)

The total output of the mammillary bodies gathers in the principal mammillary tract and divides into the descending mammillo-tegmental tract (MTT) and the ascending mammillo-thalamic tract (MMT). In the descending MTT, the medial MB sends projections back to the ventral dorsal tegmental nucleus and the lateral MB sends projections back to the lateral dorsal tegmental nucleus, thus reciprocating the projections (Swanson, 1987).

In the ascending MMT, the projections to the thalamus are exclusive to the AT sub-nuclei (Shibata, 1992). The medial MB innervates both the AV and AM thalamic nuclei on the ipsilateral side of the brain, while the lateral MB exclusively innervate the AD nucleus (bilaterally). The medial MB consists of two large subdivisions; the lateral and medial nuclei. Additionally four main subdivisions exist in the medial MB based on differences in cell sizes and densities, these are the pars medialis centralis, pars medialis dorsalis, pars lateralis, and pars basalis (Seki & Zyo, 1984). Within the medial MB, inputs from the lateral segment terminate in the AV and inputs from the medial segment terminate in the AM (Seki & Zyo, 1984; Shibata, 1992). The rostral AM receives input from the more ventral region of the pars mediana, while the dorsal region of the pars mediana has a strong projection to the IAM. The dorsomedial region of the pars lateralis projects to the ventral AM. The ventrolateral region of the pars lateralis projects to the ventral AV with a rostrocaudal arrangement; rostral cells project to rostral ventral AV, whereas caudal cells project to the caudal ventral AV. The pars basalis projects bilaterally to the dorsolateral AV; there are also a few terminal fields in the AD. Dorsal and ventral cells in the pars medialis project, respectively, to the caudal and the rostral parts of the dorsomedial AM (Seki & Zyo, 1984; Shibata, 1992).

The Amygdaloid complex

The medial thalamic nuclei with the heaviest amygdaloid projections include the mediodorsal and the midline nuclei. Within the amygdala, the different sets of amygdaloid groupings project in different patterns to the thalamic nuclei. Additionally, it appears that the projections

from the amygdala to the thalamus are not reciprocated within the same sets of nuclei (Reardon & Mitrofanis, 2000).

The amygdaloid complex projects to MDn (Krettek & Price, 1977) but only densely to the medial, magnocellular MDn region in monkeys and medial segment of MDn in non-primates. These projections from the amygdala to the medial MDn are much sparser than the amygdaloid projections to the striatum and PFC. Krettek & Price (1977) reported that the fibres from the caudal part of amygdala terminate rostrally in medial MDn and those from the rostral part terminate more caudally and ventrally in the medial MDn. However, this evidence could not be confirmed by Groenewegen et al (1990) due to their sparse projections from amygdala to medial MDn. There are also amygdaloid complex projections to the midline and some intralaminar nuclei. According to Van der Werf et al (2002) inputs from the amygdala to the PV originate in the central nucleus; the central nucleus also innervates the medial segment of the MDn, IMD and CeM (Groenewegen et al, 1990; Krettek & Price, 1977; Pitkanen, 2000; Reardon & Mitrofanis, 2000). There are significant projections from the medial nucleus to the more middle to caudal region of the PC / CeM nuclei (Reardon & Mitrofanis, 2000), although there were no projections noted to the PV and MDn as previously reported (Krettek & Price, 1977; Pitkanen, 2000). The anterior cortical nucleus and amygdaloid-hippocampal transitional area (olfactory nuclei) innervate the PT, medial MDn, IAM, CeM, and Re nuclei. The basolateral grouping of the amygdala also projects richly to the medial segment of the MDn, with a few additional terminals in PV, IAM (Krettek & Price, 1977; Pitkanen, 2000; Reardon & Mitrofanis, 2000).

The projections of the amygdala to the thalamus indicate that it does not exert a global influence on thalamic functioning but rather influences discrete thalamic nuclei and consequently thalamo-cortical pathways proposed to be involved with emotion, memory and viscero-sensation processing (Jones, 1985).

The Basal Forebrain

A significant amount of thalamic neuromodulatory input is received from the basal forebrain. Amongst many studies it is reported that the largest amount of basal forebrain inputs reaching the medial thalamus terminate in the reticular nucleus, with moderate terminal fields in the MDn and sparse terminals in the ILn, AT and LD (Hallanger et al, 1987; Parent et al, 1988; Asanuma, 1997). Within the MDn, fibres deriving from the basal forebrain are concentrated in the medial segment (Groenewegen, 1988). The basal forebrain projections to the thalamus are

predominantly GABAergic. It is the brainstem projections that provide cholinergic projections (Hallanger et al, 1987). For example, in cats, only 7-20% of basal forebrain neurons projecting to the MDn and AT are cholinergic (cited in Bentivoglio et al, 1993). In rats, both GABAergic and cholinergic terminal fields projecting from the basal forebrain are present in the reticular nucleus (Asanuma, 1997; Hallanger et al, 1987; Levey et al, 1987). The central segment of MDn receives afferents from nucleus of the diagonal band of Broca, the lateral preoptic and the lateral hypothalamus (Groenewegen, 1988).

It is noted in the neuroanatomical tracing report of Reardon and Mitrofanis (2000) that for the most part the amygdala, basal forebrain and brainstem (see section 6.5 below) project to similar areas within the medial thalamus. Therefore, it would seem that these projection sites, including the reticular nucleus, midline, ILn and MDn nuclei process and relay functionally diverse subcortical information to the cerebral cortex.

Intra-system connections of the Limbic System

Within the limbic system there are many interconnections between the hippocampal regions, the subicular complex, the posterior cingulate / retrosplenial cortex, entorhinal and perirhinal cortices, the amygdala and septum. The objective of this thesis is to highlight the interconnections of the medial thalamus with these regions, however this by itself would be insufficient to establish the functional significance of the overall system. Therefore a brief summary of intra-limbic system connections follows.

As previously mentioned, the subiculum is one of the major outputs of the hippocampal formation and sends projections to a number of cortical and subcortical structures. The subiculum receives a massive input from hippocampal area CA1, and in turn sends very dense projections to the pre- and para-subiculum, however their projections back to the subiculum are only modest (O'Mara et al, 2001). The para-subiculum has a fairly substantial projection to the molecular layer of the dentate gyrus, and like the lighter projection from the pre-subiculum, this projection occupies the superficial two thirds of the molecular layer. Amaral & Witter (1995) note that because the para-subiculum receives a projection from the AT, its projection to the molecular layer of the dentate gyrus provides a route by which thalamic input may influence very early stages of hippocampal information processing.

Cortically, the subiculum projects heavily to the retrosplenial cortex, but this connection is not reciprocal (Wyss & van Groen, 1992). There is also a substantial projection to the perirhinal cortex terminating in both superficial and deep layers, which is reciprocal (Amaral &

Witter, 1995). All subicular regions project to the entorhinal cortex (ENT). The major projection from subiculum to entorhinal cortex terminates in the deeper layers (layer IV) of medial and lateral ENT, where it is proposed to be able to interact with projections from entorhinal cortex to septum, nucleus accumbens and frontal cortex (O'Mara et al, 2001). There are also weaker projections to the superficial layers of ENT (Witter et al, 1989). The dorsal pre-subiculum projections to the ENT terminate in the deep layers IV-VI, whereas the ventral pre-subiculum projects to layers I and III, and para-subiculum project to layer II. Therefore it is assumed that these subicular regions serve different roles in processing and integration limbic system information (van Groen & Wyss, 1990).

Ventral subiculum and dorsal and ventral pre-subiculum densely innervate the retrosplenial cortex Rga, while dorsal subiculum and dorsal pre-subiculum densely innervate Rgb. In contrast, Rdg is only sparsely innervated by dorsal pre-subiculum (van Groen and Wyss, 1990; 2003). Furthermore the retrosplenial cortex projects prominently to the pre-subiculum; with layer V of the retrosplenial cortex sending pathways that terminate in layers I and III-V of the pre-subiculum (van Groen & Wyss, 1990a-c). These reciprocal connections between the retrosplenial cortex and subicular complex provide additional pathways for the AT to interact with hippocampal formation functioning.

The perirhinal cortex projects to entorhinal cortex with fibres terminating preferentially in layers II and III. Retrosplenial cortex also projects to entorhinal from all of retrosplenial cortex and terminates exclusively in the most caudal portions of medial entorhinal (Wyss and van Groen, 1992). The septum projects to the entorhinal cortex too, with the horizontal limb preferentially distributing fibres in the lateral part and vertical limb and medial septum project to more medial portions, septal projections terminate densely in layer II (Amaral & Witter, 1995). The entorhinal cortex projects back to septal area, mainly to the lateral septum but also to the medial region.

Subcortically, the mammillary bodies receive massive projections from the subicular complex. The pre-subiculum and para-subiculum send fibres to both the medial and lateral mammillary nuclei, while dorsal parts of the subiculum preferentially innervate the medial nucleus via the fornix. The lateral nucleus is only sparsely innervated by the subiculum (Amaral & Witter, 1995; Swanson, 1987; Shibata, 1992). Interestingly, it is proposed that theta rhythm is critically involved in memory processing functions of the hippocampus (Vertes & Kocsis, 1997; Hasselmo, 2000). Recent electrophysiological recordings of theta activity in the MB show that these cells fire rhythmically in bursts with the theta rhythm, and this firing is

dependent upon the interaction of the hippocampus with the MB (Kocsis and Vertes, 1997; Bland et al, 1995; Kirk et al, 1996). Other limbic system inputs descend via the medial forebrain bundle to reach the MB. The lateral septal nucleus and the bed nucleus of the stria terminalis (which receives massive input from the amygdala) preferentially innervate the lateral MB, while the medial septal-diagonal band complex preferentially innervates the medial MB. The medial preoptic area also projects significantly to the MB conveying visual and auditory information; this is the only hypothalamic input to MB (Swanson, 1987).

There are substantial interconnections between the hippocampus, subiculuar complex, and the entorhinal and perirhinal cortices and the amygdala (Amaral & Witter, 1995; Krettek & Price, 1977; Pitkanen, 2000; Price et al, 1987; van Groen & Wyss, 1990a).

Finally, the septal area projects to all fields of the hippocampus, the DG and the subicular complex via four routes: through the fimbria, dorsal fornix, supracallosal stria and ventrally, through and around the amygdaloid complex (Amaral & Price, 1995). The projections from the basal forebrain are the main source of cholinergic input to the hippocampus (Swanson et al, 1987).

A Summary of Limbic System Interconnections

The limbic system components are preferentially connected with both the anterior and midline thalamic nuclei. Additionally there are substantial interconnections between the amygdala and the MDn, especially the medial segment, as well as links with the midline nuclei. The AT is strongly with the hippocampus via the retro-hippocampal region, the mammillary bodies and the retrosplenial cortex. Together these structures form a circuit of interconnected brain regions, first described by Papez (1937; see Chapter 2). Furthermore the interconnections between the AT and retrosplenial cortex form a cortical loop in the extended hippocampal system. Briefly, Rga and Rgb receive thalamocortical projections from the AD, but the cortico-thalamic projections from Rga, Rgb, Rdg to the AD are relatively weak. Rga and Rgb have heavy reciprocal interconnections with the AV, and Rdg has dense interconnections with the AM (Shibata, 1998).

In contrast, to the AT, the functional significance between the midline nuclei and limbic system is harder to evaluate because the interconnections are more diffuse within the limbic system. In addition, the connections established by the midline nuclei with the limbic system are not exclusive as the other limbic system regions are already interconnected with each other, for example the hippocampus and the amygdala form their own interconnected system (Witter

et al, 1989; Amaral & Witter, 1995). The midline nuclei receive a variety of inputs from the hypothalamus, and brainstem (see section 6.5) and it has been proposed that the key functional roles of the midline thalamic nuclei are in the transmission of visceral sensory information, and with the regulating the behavioural state of the mammal (Swanson, 1987; van der Werf et al, 2002).

The prominent neural connections of the MDn are with the amygdaloid complex and the basal forebrain of the limbic system. In contrast, the ILn has only very sparse projections to the pre-subiculum and perirhinal cortex.

6.3 Frontal Cortex System Connections

This region includes the precentral and medial agranular cortices, dorsal and ventral anterior cingulate cortex, dorsal and ventral prelimbic, and infralimbic cortices, the medial orbital region and dorsal and ventral regions of the agranular insular cortex.

Frontal – Sub-cortical Neural Connections

There are widely regarded neural connections involving the frontal cortex and subcortical structures that form functionally segregated circuits, which are proposed to mediate specific forms of motor activity and behaviour in humans (Alexander et al, 1986; 1990; Tekin & Cummings, 2002) and animals (Groenewegen et al, 1990). The main anatomical structures are the same for all circuits. The main pathway of each circuit originates in the prefrontal cortex, projects to the striatum, and connects with the pallidus and then onto the thalamus. The final link in these circuits is a connection from the thalamus back to the prefrontal cortex. Researchers have also identified an indirect feedback pathway between the striatum, pallidum and subthalamic nucleus and back to the pallidum (Alexander et al, 1986; 1990; Groenewegen et al, 1990; Tekin & Cummings, 2002). All identified circuits are labelled after their respective prefrontal cortex areas. The principal network circuits in humans are the motor circuit, the oculomotor circuit, the dorsolateral prefrontal circuit, the lateral (and medial) orbitofrontal 'limbic' circuits, and the anterior cingulate circuit (Alexander et al 1986; 1990; Haber et al, 1990; Tekin & Cummings, 2002). In rats, similar circuits have been labelled the "dorsal agranular insular circuit", "ventral agranular insular circuit", "prelimbic circuit", and the "dorsal anterior cingulate circuit" (Groenewegen et al, 1990). It is noted that these circuits are not closed loops; there are projections both to and from various cortical and sub-cortical structures throughout the circuits. Details of the significant structures related to these cortico-striatal-pallidal-thalamic circuits will be discussed below, with special emphasis on the interconnections of the medial thalamic nuclei within these circuits. An overview of the significant neural connections and density ratings of the medial thalamus and frontal cortex system structures are presented in Table 5 (p. 95-96) with further details of firstly the efferents of thalamic nuclei to the frontal cortex. This is followed by details of the afferents to thalamic nuclei between the frontal cortical regions. In the subsequent section (6.4) the basal ganglia (striatal-pallidal-thalamic) interconnections are reviewed.

Table 5a. Frontal System Connections showing the Efferents of the Medial Thalamic Nuclei

	AVd	AVv	AMdl	AMvm	AD	LD	CL	PC	MDl	MDpl	MDm rostral	MDm caudal	MDc	CM rostral	CM caudal	IMD	PV	PT	IAM	Re	PrCm	dAC	vAC	dPL	vPL	IL	MO	dAI	vAI	VO/VLO/LO
AVd	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
AVv	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
AMdl	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	3r	3r	2	2	--	--	--	--	--
AMvm	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	3	3r	3	2	--	3	--	--	--
AD	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
LD	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	2c	2	2	--	--	--	--	--	--	--
CL	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	3m l	2	--	--	--	--	--	--	--	--
PC	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	2	3	1	2	--	--	--	C*	--	C*
MDl	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	3	3	3	1	--	--	--	--	1d	3
MDpl	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	3	3	--	--	--	--	--	--	--	--
MDm rtrl	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	2	3	M3	M3	--	--	--
MDm cdl	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	V3	3	2	2	M3	M3	V3	M3	M2
MDc	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	1	1	--	--	--	3	3
CM rstl	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	1	3	3	3	1	--	--	I	--	--
CM cdl	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	*	--	*	--	--	--	*	*	--
IMD	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	1	1	1	2	1	3	2	--
PVA	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	1	1	3	2	1	1	1	1
PT	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	1	1	2	3	3	1	1	--
IAM	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	3r	--	3c	--	--	--	1	--	--	--
Re	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--

Table 5b. Frontal System Connections showing the Efferents to the Medial Thalamic Nuclei

	AVd	AVv	AMdl	AMvm	AD	LD	CL	PC	MDl	MDpl	MDm rostral	MDm caudal	MDc	CM rostral	CM caudal	IMD	PV	PT	IAM	Re	PrCm	dAC	vAC	dPL	vPL	IL	MO	dAI	vAI	VO/VLO/LO
PrCm	--	--	--	1	--	1	3	3	?	3	--	--	--	3	--	--	--	--	1	1	X	--	--	--	--	--	--	--	--	--
dAC	1	1	2	3	1	1	3	?	2	?	2	--	--	--	--	--	1	1	--	?	--	X	--	--	--	--	--	--	--	--
vAC	--	--	1	2	--	--	3	*	3	?	*	--	?	1	1	1	3	--	1	2	--	--	X	--	--	--	--	3	3	--
dPL	--	--	--	2	--	--	?	?	2d	?	3	3	2	2	2	2	2	2	2	2	--	3	3	X	3	3	--	3	3	--
vPL	--	--	--	*	--	--	--	--	2	?	3	3	2	2	2	2	2	2	2	2	--	3	3	3	X	3	--	3	3	--
IL	--	--	--	--	--	--	--	--	2	?	*	*	*	?	*	*	*	*	*	2	--	3	3	3	3	X	--	3	3	3mo
MO	--	--	--	--	--	--	--	--	--	?	3	--	--	?	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--
dAI	--	--	--	--	--	--	--	--	*	?	1	3	--	?	--	?	1	--	--	--	--	--	--	--	--	--	--	X	--	--
vAI	--	--	--	--	--	--	--	--	--	?	--	--	3	?	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--
VO/VLO/LO	--	--	--	--	--	--	--	--	3vo /vlo	?	3lo	3lo	3lo	?	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X

6.3.1 Thalamic Afferents of the Frontal Cortical Areas

The frontal cortex can be divided into medial and lateral PFC regions. In the rat, there are four subdivisions of the medial PFC, running dorsal to ventral, which are the medial precentral (PrCm), the anterior cingulate (ACg) with its own dorsal and ventral sub-divisions, the prelimbic (PL) and the infralimbic (IL) cortical areas. As was the case with the posterior cingulate cortex in the previous section, these medial PFC regions have also been labelled with different nomenclature. According to van Groen et al (1999) the medial PFC can be divided into two main subdivisions, called anterior infraradiata (IRα) and posterior infraradiata (IRβ) cortices. There are also three further subdivisions spreading from dorsal to ventral aspects IRaα / IRaβ, IRbα / IRbβ, and IRcα / IRcβ. IRaα corresponds to the IL cortex (Brodmann's area 25), while IRbα and IRcα correspond to most of the PL cortex (Brodmann's area 32). The very caudal aspect of IRbα, as well as IRaβ and IRbβ correspond to the ventral ACg, while the very caudal aspect of IRcα, and the IRcβ correspond to the dorsal ACg.

In the lateral PFC are the agranular insular (AI) cortex with its own dorsal and ventral subdivisions, and the orbital cortex. There are several parts of the orbital cortex: medial (MO), ventral (VO), ventrolateral (VLO).

Individual nuclei of the medial thalamus send projections to only partially overlapping areas of the medial and lateral PFC, which strongly suggests that different aggregates of the thalamus transmit different information and are thus involved in different aspects of processing information in relation to their frontal connections (Groenewegen & Uylings, 2000).

The Precentral (PrCm) Cortical Area

This cortical area is also referred to as Fr2, meaning frontal area 2 (Zilles, 1985) or Brodmann's area 8. In some neuroanatomical reports this region is also referred to as the medial agranular cortex.

The medial thalamus has many sub-nuclei that send projections to the PrCm. Within the MDn nucleus, the paralamellar segment (MDpl) and lateral segment (MDl) has reciprocal connections with PrCm (Conde et al, 1990, 1995; Groenewegen, 1988; Groenewegen et al, 1990; Ulyings & van Eden, 1990). The rostral intralaminar nuclei send dense projects from the paracentral (PC) and centrolateral (CL) nuclei. Both rostral and caudal parts of the PC terminate in the PrCm (Berendse & Groenewegen, 1991). In the rostral PC dense fibres project

to the dorsal ACg and extend into the PrCm. The terminals are densest at immediate rostrocaudal levels in layers I, and superficial V. The caudal PC project to PrCm in the more lateral aspects, with terminals in layers I and between IV-V.

It has been observed that the PrCm receives projections from a larger number of CL neurons than from neurons of the lateral MDn (Conde et al, 1990; 1995). The rostral CL projects to the medial PrCm and the adjacent medial part of the lateral agranular field. There are moderate terminals in layers III and IV and dense terminals in the deep part of layer V. The caudal CL has moderate terminals in the PrCm, with very few in layer I, and some in superficial layer V (Berendse & Groenewegen, 1991).

It has also been noted that the interanteromedial (IAM) nucleus has terminals situated densely in the rostral PrCM (van Groen et al, 1999). The ventrolateral (VL) and ventromedial (VM) nuclei of the thalamus, which are situated more laterally, and ventral to the intralaminar nuclei also project to PrCm (Conde et al, 1995).

The Anterior Cingulate Cortex (ACg)

The ACg is situated in the more dorsal parts of the medial PFC and its caudal region ends where the rostral posterior cingulate cortex begins at about the genu of the corpus callosum. There are two subdivisions in the ACg: dorsal and ventral cortical areas. Brodmann labeled this part of the cortex, area 24. The retrosplenial and visual cortical regions send projections to ACg. The projections from retrosplenial area 29 are reciprocated; cells participating in this association are located in layers II, III, and V of both areas 24 and 29 (Finch, 1993).

Of the AT, only the AM subnucleus innervates the ACg. However the projection region within the AM is quite specific, with only the more medial part adjacent to the IAM, and ventral AM projecting to both ventral and dorsal aspects of the ACg (Conde et al, 1995; van Groen et al, 1999).

The ILn also project to the ACg (Berendse & Groenewegen, 1991). The review of CeM interconnections in the rat of Van der Werf et al (2002) also reported evidence of differences in the projections of the rostral and caudal CeM within the frontal cortex system. The rostral CeM has a dense network of projection fibres terminating in the rostral two-thirds of the dorsal ACg; in layers I, V the projections are dense while in layer III, they are slight. In the caudal ACg, the terminal plexus shifts to the ventral subdivision. There are no projections from the caudal CeM to the cingulate cortices. The rostral PC also has dense fibres projecting to layers I, and superficial V of the dorsal ACg, and there are a few terminals located in layer III. The caudal

CL also projects densely to the rostral part of the dorsal ACg in layer III. The ventral aspects of the midline paraventricular nucleus (PV) also project very weakly to the ventral ACg (Berendse & Groenewegen, 1991). The VL also project to dACg (Conde et al, 1990; 1995).

The Infralimbic (IL) and Prelimbic (PL) Cortex

The IL and PL are situated more ventrally in the dorsomedial PFC, with the IL located more ventrally than the PL. There main inputs are received from medial and lateral segments of MDn, the AM, IAM, PT and PV thalamic nuclei, field CA1 of hippocampus, the subiculum, basolateral amygdala, agranular insular cortex and laterodorsal tegmental nucleus of the brainstem.

There are significant projections to the IL and PL received from many of the medial thalamic nuclei. The rostral part of the medial segment of the MDn has reciprocal connections with both the IL and PL cortical areas (Groenewegen et al 1990). In rats, the medial MDn, and in monkeys, the medial magnocellular segment of MDn projects predominantly to the PL and IL areas in the medial PFC (Groenewegen & Uylings, 2000). The lateral segment of MDn also projects substantially to PL and mildly to IL (Conde et al, 1990; 1995). The midline intermediodorsal (IMD) nucleus has dense fibres limited to the rostroventral part of the PL, involving layers I, III and superficial V (Groenewegen et al, 1990; Berendse & Groenewegen, 1991).

The caudal AM sends projections that mainly terminate in the PL (layers I and V), and these terminals also extend further rostral to sparsely innervate the ventral frontal polar cortex (layers I and V). Some terminal fields of the IAM form a small dense terminal field in caudal, ventral PL (layers I and V; van Groen et al, 1999).

The CeM nucleus of the intralaminar nuclei also project to the dorsal PL (Berendse & Groenewegen, 1991). The projections from the CeM terminate throughout the rostrocaudal extent of the dorsal part of the PL cortex amongst layers I and V and lightly to layer III. There are also projections from the paratenial (PT) nucleus that predominantly innervate the IL area. In the rostral IL the terminals are denser with projections to layers I and III and sparsely in V, whereas terminals in the caudal IL are less dense. There are also fibres terminating in the ventral part of the PL. The PV has interconnections with the ventral PL with terminal fields located mainly in layers I, V and VI (Berendse & Groenewegen, 1991; Van der Werf et al, 2002).

The Agranular Insular Cortex (AI)

At a level that is rostral to the genu of corpus callosum is the agranular strip of insular cortex, subdivided into anterior and posterior divisions. The whole of the agranular insular (AI) cortex appears to be a 'mutlimodal sensory convergence zone' for the posterior insular and piriform cortices and major efferents of the MDn-related cortical areas (Shi & Cassell, 1998).

There are extensive projections from selective segments of the MDn project to the subdivisions of the AI. The posterior, ventral part of the medial segment of MDn has reciprocal fibre connections with the dorsal AI cortex (Groenewegen, 1988). In contrast, the central segment of MDn projects densely to the ventral AI cortex; these connections are reciprocal (Groenewegen, 1988). The IMD has dense projections to the ventral part of the dorsal AI, extending throughout the rostrocaudal extent. The layers with the highest density of terminals are layers I, III and superficial V; this innervation also extends into the posterior agranular insular cortex (Berendse & Groenewegen, 1991).

There are also projections from some of the midline and intralaminar nuclei to the AI (Berendse & Groenewegen, 1991). The caudal PC sends projections to the rostral part of the dorsal AI, amongst layers I, III and V, and this projection extends into the adjacent lateral orbital cortex. In addition the most caudal aspects of the CeM project to the AI (Groenewegen, 1988; van der Werf et al, 2002). The PT also has a few terminals in the ventral AI and there are some projections from PV terminating mainly in dorsal but also ventral subdivisions.

The Orbital Cortex

There are several different areas of the orbital cortex, including the medial orbital (MO), ventral orbital (VO) and ventrolateral orbital (VLO), and lateral orbital (LO) areas.
The MO is significantly connected with the rostral part of the medial segment of MDn, while the VO and VLO cortices interact with the lateral segment and LO interacts with central and medial segments of MDn (Groenewegen et al, 1990). The AM nucleus also innervates the MO (van Groen et al, 1999).

There are some intralaminar and midline nuclei projecting to the orbital cortex. Both the rostral and caudal parts of CL project to the VLO, with denser cells projecting from the caudal part to layers I, III and V. The PT nucleus projects mainly to the dorsal part of MO amongst layers I, III, and some V (Berendse & Groenewegen, 1991).

6.3.2 Frontal cortex outputs

The Medial Precentral Cortex (PrCm)

The projections from the PrCm to the thalamus are mainly ipsilateral and pass through the internal capsule (Vertes, 2002). Within the rostral thalamus, there is moderate to dense terminal fibres projecting to the intralaminar nuclei including the CeM, PC and CL. The paralamellar segment of the MDn also receives dense projections from the PrCm. In both the ILn and MDpl nuclei, these PrCm terminal fields continue through to the caudal part of the medial thalamus. There are also fibre terminals in the midline and lateral thalamic nuclei, including the IAD, IMD, most medial AM, IAM, laterodorsal (LD), rhomboid (Rh), medial reuniens (Re), ventral anterior (VA) and ventral medial (VM) thalamic nuclei (Groenewegen et al, 1990; Uylings & van Eden, 1990; Vertes, 2002).

The Anterior Cingulate Cortex (ACg)

Within the ACg, there are topographical differences in the projections to the medial thalamus. The caudal, and not the rostral aspects of the ACg project densely to the AM and IAM, especially the ventral AM. In addition, the ventral rather than dorsal aspects produce denser labelling in PV, MDc, IMD, CeM and ventrolateral aspects of the lateral MDn (Groenewegen et al, 1990, 1991; Vertes, 2002). The projections from the ACg to the thalamus are also mainly ipsilateral and pass through the internal capsule (Vertes, 2002). Specifically, in the rostral thalamus, the ACg fibres terminate densely in AM (particularly in AMv but also AMd), PT, IAM, and Re; moderately in the lateral segment of the MDn as well as PV and Rh; and lightly in rostral aspects of the AD, AV and Rt nuclei of the thalamus. In the more caudal aspects of the rostral thalamus, the AM continues to be innervated as well as PV, IAM, lateral MDn, CL, CeM, dorsal LD, Rh and ventral Re. There are also ACg axons that appeared to course through but not terminate in AV en route to the lateral segment of MDn. In the caudal thalamus, light terminal fields are also located in the CeM, IMD, PV, parafascicular nucleus (Pf), while the dense terminal fields continue in the lateral MDn and dorsal CL (Groenewegen et al, 1990, 1991; Vertes, 2002).

The Infralimbic (IL) and Prelimbic (PL) Cortex

The IL and PL projections are commonly distributed to nuclei of the medial thalamus (Vertes, 2004). Both the IL and PL project to the midline and medial thalamus, with very few fibres in

the lateral areas. The IL and PL axons terminate densely in all segments of the MDn but in the caudal thalamus terminals in the lateral and central segments are only lightly labelled. There is also moderate to heavy terminal fields in the midline nuclei, including the PT, PV, IAM, Re, CeM and IMD. In addition, the PL also project to the ventral AM nucleus, with caudal rather than rostral aspects providing heavier innervation (Groenewegen et al, 1990; Vertes, 2002; 2004).

The Agranular Insular Cortex (AI)

The ventral AI has significant connections with the central segment of the MDn, with no labelling noted in the medial segment (Shi & Cassell, 1998; Uylings & van Eden, 1990). In contrast, the dorsal AI has significant connections with the middle and caudal parts of the medial segment of the MDn (Groenewegen et al, 1990); there are also a few scattered terminal fibres in the adjacent PV (Shi & Cassell, 1998).

The Orbital Cortex (MO, VO, VLO, LO)

The MO is significantly connected with the rostral part of the medial segment of MDn, while the VO and VLO interact with the lateral segment of the MDn and the LO interacts with central and medial segments of MDn (Groenewegen et al, 1990).

Intra- and Inter-system connections of the Frontal Cortex

The PL, IL and ACg project to the limbic system cortical areas and the projections are reciprocal (Conde et al, 1995; Wyss & van Groen, 1992; Vertes, 2002, 2004). The innervations to the entorhinal cortex terminate preferentially in the rostral portions directly ventral to the rhinal fissure. Cortical inputs to the retrosplenial cortex show that Rga receives inputs mainly from the ventral AC, while the dorsal AC primarily innervates Rgb and Rdg (van Groen and Wyss, 1990; 1992; 2003). In addition, the IL, PL, and ventral ACg project to the dorsal and ventral agranular insular cortices. The IL projects to PL, ACg, medial frontal pole and the MO cortex, while the PL also projects to ACg, medial frontal pole, MO and IL.

The subiculum projects heavily to the medial PFC, particularly the MO and VO, as well as the PL and IL cortex. It also sparsely innervates the ACg (Wyss & van Groen, 1992; Amaral & Witter, 1995).

The IL (Takagishi & Chiba, 1991; Vertes, 2004) also innervates the basal forebrain, olfactory system, preoptic area and hypothalamus. The PL also sends significant innervations

to the C-Pu and nucleus accumbens (core and shell) as well as the olfactory tubercle and claustrum in the basal forebrain and some olfactory system projections are also apparent (Vertes, 2004).

Frontal Cortical Areas and Amygdala Interconnections

There are significant interconnections between the amygdala and the frontal cortex systems too. The dorsal AI projects densely to the rostral half of the lateral, basolateral, anterior basomedial and anterior cortical nuclei of the amygdala, with a few fibres scattered in the central nucleus. The ventral AI has light to moderate terminal fields in the central, lateral, basolateral and ventral endopiriform nuclei and layer II of the posterior piriform cortex (Shi & Cassell, 1998). The prefrontal cortex projects to the caudal part of the basolateral nuclei, with moderate to heavier projections from infralimbic, precentral and both dorsal and ventral agranular insular cortex, and lighter projections from the prelimbic region. The lateral nucleus of the amygdala reciprocates projections to the ventral AI, infralimbic cortex as well as lighter connections back to the prelimbic (Pitkanen, 2000). The IL also project to medial, basomedial, cortical and central nuclei and the PL also project to the central nucleus.

Summary of Frontal system connections

The PFC in mammals has been defined by the projections received from the MDn since the earlier discoveries of Rose and Woolsey (1948; cited in Ulyings & van Eden, 1990). Many recent neuroanatomical tracing studies have confirmed the strong reciprocal connections between the MDn and the PFC, and have identified that the interconnections are relatively similar between rats and primates (Ulyings & van Eden, 1990; Ulyings et al, 2003). In addition, these recent studies have provided evidence for strong interconnections with other medial thalamic nuclei, including the ILN and the AM nucleus of the AT. Furthermore, the thalamic projections to the PFC represent in many instances the final link in fronto-stratial-pallido-thalamic circuits (Alexander et al, 1986; Groenewegen et al, 1990; 1999). The following section 6.4 will detail the striatal-pallido-thalamic interconnections.

6.4 Basal Ganglia Complex Connections

This region includes the nucleus accumbens (core and shell), the caudate-putamen (also referred to as the striatum), globus pallidus, ventral pallidum and olfactory tubercle. The amygdala connections have already been described in the limbic system sections (6.2). As discussed in section 6.3, the basal ganglia complex is incorporated into the fronto-striatal-pallido-thalamic circuits. Within the basal ganglia neurochemically and anatomically differentiated regions have been identified called the striatal patch and matrix (Gerfen, 1992). Neurochemically, both patch and matrix regions receive dopaminergic inputs, although from different regions, with the patch receiving inputs originating in the ventral tegmental area and substantia nigra projecting to the matrix. Anatomically, corticostriatal and thalamostriatal projections are closely associated with the striatal matrix, while projections from the limbic structures to the striatum (e.g. the hippocampus and amygdala) appear to primarily innvervate the striatal patches. It is proposed that the striatal matrix primarily mediates the mnemonic functions of the dorsal striatum (White 1989). Thus the connections of the striatal matrix are of particular interest in the current thesis. These projections of the midline and intralaminar nuclei to the striatum constitute one of the two major striatal inputs. The other major input to the basal ganglia is derived from the entire cortical mantle, which is topographical arranged in that functionally different cortical areas project to separate striatal regions with very little overlap (Berendse & Groenewegen, 1991).

The significant outputs of these regions are directed towards different parts of the thalamus, subthalamic nuclei and midbrain / brainstem. These differences in output connections also suggest these striatal regions are functionally distinct. Table 6 (p. 105-106) includes a summary of the thalamic connections with the basal ganglia complex and density ratings of those connections.

Table 6a. Basal Ganglia Complex Afferent Connections from the Medial Thalamic Nuclei

	AVd	AVv	AMdl	AMvm	AD	LD	CL	PC	MDl	MDpl	MDm rtrl	MDm cdl	MDc	CeM rstl	CeM cdl	IMD	PV	PT	IAM	Re	Acb core	Acb shell	C-Pu dm	C-Pu dl	C-Pu vlrl	GP mdl	GP cdl	VP	OT
AVd	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
AVv	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
AMdl	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
AMvm	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	1	--	--	--	--	--	--
AD	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
LD	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	1	1	--	--	--	--	--
CL	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	1	3	--	--	--	--	--
PC	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	1	1	3	2	1	1v	--	1	1
MDl	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	2	--	--	--	--	--	--
MDpl	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
MDm rstl	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
MDm caudal	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
MDc	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
CeM rstl	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	2r	--	3	3	--	--	--	--	--
CeM caudal	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	1	--	3	--	--	*	*r
IMD	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	3	1	1	--	3	1v	--	2	1
PV	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	2	3m	1	--	2	--	--	1	3
PT	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	1	2v r	1	--	1	--	--	1	3
IAM	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--
Re	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--

Table 6b. Basal Ganglia Complex Efferent Connections to the Medial Thalamic Nuclei

	AVd	AVv	AMdl	AMvm	AD	LD	CL	PC	MDl	MDpl	MDm rtrl	MDm cdl	MDc	CeM rstl	CeM cdl	IMD	PV	PT	IAM	Re	Acb core	Acb shell	C-Pu dm	C-Pu dl	C-Pu vtrl	GP mdl	GP cdl	VP	OT
Acb core	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	–	–	–	–	3	–
Acb shell	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	–	–	–	3	–
C-Pu dm	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	–	–	–	–
C-Pu dl	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	–	–	–
C-Pu vtrl	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	–	–
GP mdl	–	–	–	–	–	–	1	1	3	3	–	2	–	2	–	–	–	–	–	–	–	–	–	–	–	X	–	–	–
GP cdl	–	–	–	–	–	–	–	–	*	*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–
VP	–	–	–	–	–	–	–	1	–	–	M3	L3	–	1	1	–	–	–	–	–	3	3	–	–	–	–	–	X	–
OT	–	–	–	–	–	–	–	–	–	–	–	–	3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	St3 pl

6.4.1 Thalamic Afferents of the Basal Ganglia Complex

The Caudate-Putamen (C-Pu)

The most extensive projections to the C-Pu originate from midline and intralaminar thalamic nuclei to the C-Pu. These projections run in a topographical manner, with the rostral parts of a nucleus projecting to more rostral parts of the C-Pu. There is also a rostral to caudal dimension within the projection nuclei, which corresponds to a dorsal to ventral dimension in the C-Pu (Berendse & Groenewegen, 1991; Erro et al, 2002). The rostral CeM projects extensively to the rostral regions of C-Pu in the medial part while more caudally it extends to only the very dorsomedial part of the caudate-putamen complex. The caudal CeM has extensive projections to the ventrolateral striatum, i.e. the fundus striatum. The PC and CL send fibre terminals to successively more lateral parts of the C-Pu, respectively. As the projections extend throughout the rostrocaudal extent of the C-Pu, they transfer from a more dorsomedial to ventrolateral topography. In addition, the lateral part of the parafascicular (Pf) nucleus of the caudal grouping of the ILn projects to the most lateral part of the C-Pu, while the medial Pf nucleus projects to the most medial part of the C-Pu (Berendse & Groenewegen, 1990; 1991; Groenewegen et al, 1999). The IMD has extensive projections with the entire rostrocaudal extent of the ventral C-Pu, while the PV and PT send fibres to the area of caudate-putamen adjacent to the shell (i.e. the most ventral, medial and caudal parts of the C-Pu; Berendse & Groenewegen, 1990; 1991).

In addition, the lateral segment of the MDn also projects to dorsomedial striatum and projections from the LD and lateroposterior (LP) nucleus terminate in the most dorsal part of the C-Pu (Cheatwood et al, 2003). There is also a C-Pu projection that exists from the AM nucleus of the AT. Van Groen and colleagues (van Groen et al, 1999) reported that from the caudal most part of AM, there are a few axons synapsing in the dorsomedial corner of C-Pu.

The Ventral Striatum (VS) and Nucleus Accumbens (Acb)

Within the VS lies the nucleus accumbens (Acb); a nuclear mass in the rostroventral part of the VS, bordered medially by the septum and ventrally by the olfactory tubercle. According to Packard and Knowlton (2002) it was Heimer and colleagues (Heimer & Van Hoesen 1979) who adopted the term ventral striatum to delineate the most ventral aspects of the striatum (i.e. nucleus accumbens and portions of the olfactory tubercle) from more dorsal regions (i.e. the caudate nucleus or dorsal striatum).

It has been proposed that the Acb form an integral part of the striatum, in which limbic and motor projections interact (Mogenson et al, 1980). More recently the Acb has been linked with affective disorders, such as schizophrenia and drug abuse (Robbins & Everitt, 1996). The Acb is divided into a core and a shell region, based on differential distributions in the Acb of the calcium-binding protein, calbindin (Groenewegen et al, 1999). The Acb receives inputs from a variety of regions, including the hippocampal region, basal amygdaloid complex, medial thalamus, ventral pallidum and brainstem dopaminergic and serotonergic regions. The midline nuclei including the IMD, PT, and PV send dense terminals to the VS, while the intralaminar nuclei projects to the VS to a lesser degree (Berendse & Groenewegen, 1990; Erro et al, 2002). Within the VS, the core and shell of the Acb have some relatively distinct patterns of interconnections with these brain regions so these will be discussed separately below.

The Core Region of the Nucleus Accumbens (Acb)

The core region of the Acb is represented in its more central and more dorsal parts. The medial thalamus projects to the nucleus accumbens core; these projections originate in the ILn and midline nuclei. The PV and PT project sparsely to the core region. The IMD projects throughout the nucleus accumbens, with substantial inputs to the core region (Berendse & Groenewegen, 1990; 1991; Groenewegen et al, 1999). In addition, a review of CeM interconnections in the rat (van der Werf et al, 2002) reported evidence of differences in the projections of the rostral and caudal CeM within the basal ganglia complex. The rostral CeM projects to the Acb, with fibre terminals concentrated in the core throughout the rostrocaudal extent, while the caudal CeM does not project to the Acb at all.

The Shell Region of the Nucleus Accumbens (Acb)

The shell region of the Acb is located in its more medial through to caudal aspects, as well as the ventral and lateral parts of the Acb. The projections from the PT nucleus include predominantly the ventral and rostral parts of the shell, avoiding its most medial and lateral parts (Groenewegen et al, 1999). The anterior part of the PV has a strong projection to the medial shell of the Acb, while the more posterior parts of PV send fibres to more ventral and lateral parts of the shell (Su & Bentivoglio, 1990; Groenewegen et al, 1999). The caudal PC has light terminal fibres projecting to the posterolateral shell regions of the Acb (Berendse & Groenewegen, 1990; 1991).

The Olfactory tubercle (OT)

The IMD projects to the OT, with terminals located in layer I (Berendse & Groenewegen, 1990; 1991).

The Globus Pallidus (GP)

Within the dorsal pallidal complex there are two obvious segments, an external segment, representing the main body of the GP and an internal segment, called the entopeduncular nucleus (Groenewegen et al, 1990). As far as I am aware there are no neuroanatomical tracing studies that document direct projections from the medial thalamus to the GP. Instead the medial thalamic influences the GP indirectly via projections from the striatum.

The Ventral Pallidum (VP)

Within the ventral pallidal complex there are differences in the neurons and fibres, which may be comparable to an external and an internal segment (cf. the globus pallidus), however the distinction is not obvious (Groenewegen et al, 1990, 1991). There are two separate output projections originating from the VP as well, one to the medial thalamus and habenula, and the other to the subthalamic nucleus and the substantia nigra (Groenewegen et al, 1990). As far as I am aware there are no neuroanatomical tracing studies that document direct projections from the medial thalamus to the VP.

6.4.2 Basal Ganglia Complex Outputs

There are no neuroanatomical tracing studies that document direct projections from the C-Pu to the medial thalamus in rats, or in primates and humans. Instead the C-Pu projects to the output structures of the pallidum via either direct or indirect pathways and then onto the medial and ventral thalamus. The direct pathway comprises of striatal projections to the internal segment of the GP and the reticular part of the substantia nigra (located in the brainstem) then to the thalamus. The indirect pathway comprises of striatal projections to the external segment of the GP, then to the subthalamic nucleus, which in turn project to the internal segment of the GP and the reticular part of the substantia nigra, and then to the thalamus[1] (Groenewegen et al, 1999; Saint-Cyr, 2003).

[1] In the direct pathway, the neurotransmitter GABA is activated, which inhibits pallidal and nigral neurons and consequently disinhibits the thalamus and midbrain targets. In the traditional model, it is proposed that this

Nucleus Accumbens (Acb) Core

The core of the Acb projects to the medial thalamus via a relay in the dorsomedial part of the substantia nigra pars reticulata. The projections to PC and CeM nuclei of the ILn and the ventromedial (VM) nucleus are very dense, while those to the MDn are very light (Groenewegen et al, 1999).

Nucleus Accumbens (Acb) Shell

The shell of the Acb projects to the medial thalamus via the ventral pallidum. The projections to the MDn are very dense, while in contrast those to the PC and CeM nuclei of the ILn and VM nucleus are very light (Groenewegen et al, 1999).

The Olfactory tubercle (OT)

The central segment of MDn has its most strong and specific input from olfactory related structures, such as the deep layers of the pre-piriform cortex and the ventral pallidal cells in the OT (Groenewegen, 1988; Groenewegen et al, 1990).

The Globus pallidus (GP)

Within the GP, the internal segment is the main direct output site to the thalamus. The internal segment of the GP projects predominantly to the lateral segment of the MDn (Groenewegen et al, 1990).

Ventral pallidum (VP)

The medial, shell-innervated VP projects densely to the medial segment of the MDn and the rostroventral part of the reticular nucleus. There are also lighter projections to the CeM and PC

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pathway facilitates thalamocortical activity and facilitates behavioural and motor outputs. The cells express mainly dopamine D1 receptors in the direct pathway. In the indirect pathway, the neurotransmitters GABA and glutamate are activated. The GABA inhibits the pallidal neurons, which leads to less inhibition at the subthalamic level where glutamate has stronger activity levels as a result. The glutamate then influences GABA in the output neurons of the internal segment of globus pallidus and pars reticulata of the SN, which results in stronger inhibition of the thalamic and midbrain targets. It is proposed this indirect pathway then exerts an inhibitory influence on the thalamus and midbrain, equating to suppression of behavioural and motor outputs. The cells express mainly dopamine D2 receptors in the indirect pathway. These two hypotheses on the direct and indirect pathway modulation are particularly relevant to theories of motor output problems associated with Parkinson's and Huntingdon's diseases (Tekin & Cummings, 2002).

nuclei of the ILn as well as the nucleus reuniens and medial part of the VM nucleus (Groenewegen et al, 1999).

Inter- and Intra-system Connections

Other major inputs to the basal ganglia complex originate in the frontal cortex and the amygdaloid complex. Through the MDn the PFC receives information processed by the basal ganglia, but the PFC sends projections directly to basal ganglia structures as well. The PFC projects in a topographical arrangement with the striatum and there is some overlap in terminal fields in the striatum of fibres from individual PFC areas (Groenewegen et al, 1990). The dorsoventral axis in the medial PFC is maintained in these projections. The medial precentral cortex (PrCm / Fr2) and the ACg project to the dorsocentral and the dorsomedial areas of the C-Pu complex, respectively. The ventral part of PL sends fibres to the dorsomedial part of the shell, as well as to the patches of the Acb core. It is a similar arrangement for dorsal PL, but the projections from dorsal PL area extend further rostrally into the Acb and more dorsally into the medial caudate-putamen than those from the ventral PL area. The IL projects to a peripheral, band-like region in the medial and ventral parts of the shell, as well as the lateral part of the medial shell and the medial part of the core of the Acb (Cheatwood et al, 2003; Sesak et al, 1989; Groenewegen et al, 1990; 1999; Vertes, 2004).

There is also a medial-to-lateral topography: the medial PFC sends fibres to the more medial parts of the striatum, while the lateral PFC distributes its fibres in the more lateral parts of the striatum complex. The lateral shell of the Acb receives its cortical inputs predominantly from the ventral AI area in the depth of the rostral part of the rhinal sulcus, while the dorsal AI project predominantly to the core of the Acb and extensive parts of the ventral caudate-putamen. Projections from the dorsal AI and dorsal PL overlap in caudal parts of the Acb core, but the dorsal PL area tends to project more medially and rostrally in the Acb than the dorsal AI area (Groenewegen et al, 1999).

Within the basal ganglia complex there are topographically organised projections from striatal to pallidal areas. Both the dorsal and ventral striatum confirm a general notion of strict dorsal-to-ventral, rostral-to-caudal, and medial-to-lateral topographical arrangements. The connections are also reciprocal. The medial shell and the core project to the ventromedial and the dorsal parts of the ventral pallidum, respectively. The lateral shell projects to the ventrolateral part of the ventral pallidum. The striatal parts of the OT project to the pallidal

parts of the OT and they maintain a medial to lateral topography (Groenewegen et al, 1990; Groenewegen et al, 1999).

The hippocampal region also projects to the Acb. The entorhinal cortex projects to the striatum, mainly the ventral portions (nucleus accumbens and olfactory tubercle). These projections originate in layer V of entorhinal cortex and are topographically organised, such that medial parts of entorhinal project to caudomedial nucleus accumbens and lateral entorhinal projects to lateral nucleus accumbens (Amaral & Witter, 1995).

There are also significant inputs from the amygdala. These projections mainly originate in the basal amygdaloid complex, but other amygdaloid nuclei also contribute with denser projections to the ventral striatum, and the caudal part of the caudate-putamen complex, with a less dense projection to the rest of the caudate-putamen complex (Groenewegen et al, 1999c; Krettek and Price, 1977; McDonald, 1998). The globus pallidus also sends a dense projection to the lateral nucleus of the amygdala (Pitkanen, 2000).

Summary of Basal Ganglia Complex Connections

There are clear projections running from the ventral pallidum to the thalamus that project further to the prefrontal cortex. There are also significant connections from the ventral striatum and pallidal regions with different nuclei within these regions projecting to other brain structures, including the thalamus. In addition, different areas of the prefrontal cortex project back to the striatum and therefore complete many different fronto-striatal-pallidal-thalamic circuits, with specific feedback loops (Alexander et al, 1986; Groenewegen et al, 1990; 1999a-b). It appears that the predominantly segregated circuits traversing through the shell and the core of the Acb converge in parts of the thalamus, although 'with relatively little overlap', before projecting onto different layers of the medial PFC (Groenewegen et al, 1999).

Identification of basal ganglia-thalamocortical circuits in the rat

According to Groenewegen et al (1990; 1999), there are four basal ganglia-thalamocortical circuits within the rat brain, with the possibility of extensions to these circuits as neuroanatomical tracing techniques become more advanced. One of the circuits involves the dorsal anterior cingulate in the medial PFC and also includes the dorsomedial C-Pu, the medial GP, and the lateral segment of the MDn. The prelimbic and ventral anterior cingulate areas in the medial PFC form the cortical nodal point in another circuit that includes the medial part of

the Acb (core), the medial part of VP, and rostral part of the medial segment of the MDn. Another circuit involving the lateral PFC area of the ventral agranular insular cortex includes the striatal and pallidal aspects of the olfactory tubercle and the central segment of the MDn. The fourth circuit incorporates the dorsal agranular insular cortex in the lateral PFC as well as the lateral part of the Acb, the lateral part of the VP and the caudal part of the medial segment of the MDn, with perhaps the IMD included in this circuit also (Groenewegen et al, 1990). These anatomical circuits involving the MDn help to form the basis for the hypotheses of the current thesis that distinct medial thalamic nuclei form different aggregates that have distinct interconnections with multiple memory systems of the brain.

6.5 Midbrain / Brainstem Connections

The regions of interest relate to the neuromodulatory systems that originate in the midbrain / brainstem and influence the medial thalamus. These include the laterodorsal tegmental (LDTg) and peduncular pontine tegmental (PPT) nuclei (cholinergic fibres) of the tegmentum, the locus coeruleus (noradrenergic fibres), the dorsal and central raphe nucleus (serotonergic fibres), and the substantia nigra and the ventral tegmental area (dopaminergic fibres). Projections from the reticular system are also detailed. The midbrain and brainstem receive extensive projections from many regions of the brain. However, the medial thalamus, which is of particular interest to this PhD, does not itself project directly to the either the midbrain or the brainstem areas. Table 7 (p. 114-115) details the neural connections of the midbrain and brainstem with the medial thalamus.

Table 7a Midbrain / Brainstem Afferent Connections from the Medial Thalamic Nuclei

	AVd	AVv	AMdl	AMvm	AD	LD	CL	PC	MDl	MDpl	MDm rostral	MDm caudal	MDc	CeM rostral	CeM caudal	IMD	PVA	PT	IAM	Re	LDTg	PPTg	LC	Dorsal Raphe	Median Raphe	VTA	SN	Reticular
AVd	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
AVv	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
AMdl	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
AMvm	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
AD	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
LD	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
CL	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
PC	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
MDl	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
MDpl	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
MDm rostral	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
MDm caudal	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
MDc	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
CM rostral	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--	--
CM caudal	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--	--
IMD	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--	--
PV	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--	--
PT	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--	--
IAM	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--	--
Re	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--	--
LDTg	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--	--
PPTg	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--	--
LC	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--	--
Dorsal Raphe	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--	--
Median Raphe	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--	--
VTA	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--	--
SN	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X	--
Reticular	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	X

Table 7b Midbrain / Brainstem Efferent Connections to the Medial Thalamic Nuclei

	AVd	AVv	AMdl	AMvm	AD	LD	CL	PC	MDl	MDpl	MDm rostral	MDm caudal	MDc	CeM rostral	CeM caudal	IMD	PVA	PT	IAM	Re	LDTg	PPTg	LC	Dorsal Raphe	Median Raphe	VTA	SN	Reticular
LDTg	3	3	--	--	1	2	2	2	2	?	--	--	--	2	2	--	1	--	--	--	X	*	--	--	3	3	*	?
PPTg	1	1	--	--	--	2	2	2	--	--	--	--	--	2	2	--	--	--	--	--	*	X	--	--	--	--	2c	--
LC	3	3	--	--	--	--	*	*	*	*	*	*	*	*	*	--	2	--	--	--	--	--	X	--	--	--	--	--
Raphe, dorsal	3	3	--	--	--	--	3	3	1	--	3	3	--	3	3	--	--	--	--	--	--	--	--	X	--	--	--	--
Raphe, median	--	--	--	--	--	--	2	1	3	--	1	1	--	2	2	--	--	--	--	--	--	--	--	--	X	--	--	--
VTA	--	--	--	--	--	--	--	--	3	3	3	3	--	--	--	--	3	--	--	--	--	--	--	--	--	X	--	--
SN	--	--	--	--	--	--	--	3	3	3	3	3	--	3	3	--	3	--	--	--	--	--	--	--	--	--	X	--
Reticular formation	--	--	--	--	--	--	*	*	*	*	*	*	*	*	*	--	--	--	--	--	--	--	--	--	--	--	--	X

6.5.1 Midbrain / Brainstem Inputs

The Laterodorsal Tegmental (LDTg) and Peduncular Pontine Tegmental (PPTg) Nuclei

The LDTg and PPTg are located in the mesopontine junction in the region of the brachum conjunctivum, these two structures are collective called the mesopontine tegmental nucleus. This region is characterised by its intense staining for acetylcholinesterace (AChE) and according to Shute and Lewis (1967) forms a major component of the 'ascending reticular activating system'. Within the LDTg there are two separate regions: a dorsal and a ventral component. The majority of the cholinergic cells are located in the dorsal LDTg, whereas the majority of the cells in the ventral LDTg stain positively for glutamic acid decarboxylase (GAD), and are presumably GABAergic. It is proposed that the GABA cells form local circuits in the LDTg and that the cholinergic cells are the projection neurons to other regions of the brain (Asanuma, 1997; Inglis & Semba, 1997).

Satoh & Fibiger (1986) conducted a detailed analysis of the afferent and efferent connections of the LDTg. There is much input to the LDTg including that from the mammillary bodies, the medial prefrontal cortex, the diagonal band of Broca, and the habenula nucleus in the thalamus. The medial PFC projections originate from the prelimbic, infralimbic and anterior cingulate cortices. Cornwall et al (1990) using PHA-L injections also reported projections from these medial PFC regions to the LDTg. However they suggest these projections are relatively minor, and instead projections from the orbital cortex provide the major LDTg cortical input. Others have since reported the projections from the PFC are quite substantial (Vertes, 2004).

The PPTg receive direct output from the basal ganglia, at both dorsal and ventral striatum output sites, including the globus pallidus, ventral pallidum / substantia innominata, subthalamic nuclei, substantia nigra pars reticulata and also the superior colliculus (cited in Keating & Winn, 2002).

6.5.2 Midbrain / Brainstem Outputs

The most extensive research conducted on brainstem projections to the thalamus has concentrated on the connections of the LDTg and PPTg. However, recently Krout and colleagues (Krout et al, 2000a, b, 2001, 2002) conducted an extensive analysis of brainstem

projections to the medial thalamus with particular emphasis on the midline and ILn projections. They provide evidence for each of the midline and ILn nulci being innervated most significantly by a different set of brainstem nuclei. In addition, they noted that the AT receive relative few midbrain / brainstem neuron projections. That is, the mesopontine tegmental nucleus projection is the only significant brainstem projection to ATN. Table 4 includes details of density ratings of the significant outputs from the midbrain / brainstem regions to the medial thalamic nuclei, and further details are discussed below.

The Laterodorsal Tegmental and Peduncular Pontine Tegmental Nuclei

Satoh & Fibiger (1986) reported that there are two main projection systems of the LDTg. One long projection, which courses through the dorsomedial tegmentum, diencephalon, medial forebrain bundle and diagonal band of Broca to the medial PFC. In the thalamus, the LDTg innervates the lateral habenula, parafascicular, AT, LD, lateral segment of the MDn, and intralaminar (CL, PC, CeM) nuclei. There are also sparsely labelled fibres in PV, rhomboid, ventrolateral, and reticular nuclei (Groenewegen, 1988; Satoh & Fibiger, 1986). However, the major target of the cholinergic LDTg in the medial thalamus is the AV nucleus, which stains darkly for AChE (Hallanger et al, 1987; 1990). There are also high densities of cholinergic axons in the ILn, lateral segment of the MDn and reticular nucleus (Levey et al, 1987). Within the ILn, the LDTg projects moderately to the CL, CeM and parafascicular and only lightly to the PC and midline PT areas (Krout et al, 2002). The majority of the fibre terminals to these areas are cholinergic, with axons from a single neuron innervating both sides of the thalamus (Bentivoglio & Steriade, 1990).

In the medial PFC, the LDTg terminals are located in infralimbic and anterior cingulate cortices (Cornwall et al, 1990).

The second projection from the LDTg, which is shorter, sends diffuse innervation to the median raphe, interpeduncular and lateral mammillary nuclei (Satoh & Fibiger, 1986; Swanson, 1987; Shibata, 1992).

The PPTg afferents reach the substantia nigra pars compacta, globus pallidus, subthalamic nucleus, superior colliculus and thalamus (Asanuma, 1997). In the thalamus, the PPTg projects to mainly principal thalamic relay nuclei including the ventroposteromedial, ventroposterolateral and dorsal lateral geniculate, although there are also moderate to densely labelled terminal fields in the lateral parafascicular, CL, PC, CeM, and LD nuclei (Asanuma,

1997; Erro et al, 1999; Hallanger et al, 1987). There are also some minor projections to the Re, rhomboid, and AV thalamic nuclei (Krout et al, 2002).

It has been proposed that the specific function played by cholinergic neurons of the PPTg and LDTg relates to cortical EEG activation during REM sleep and the state of wakefulness / arousal (Steriade & McCarley, 1990; Steriade et al, 1991). However, recent evidence has also indicated that the significant LDTg inputs to the VTA may modify the release of dopamine to the ventral striatum, which has reinforcing effects on behaviour (Blaha et al, 1996; Winn et al, 1997). Moreover recent evidence has indicated that the PPTg and LDTg neurons may also contribute to other behavioural processes too, including memory (Jenkins et al, 2002; Mitchell et al, 2002; Steckler et al, 1994).

The Locus Coeruleus (LC)

There is an extensive span of noradrenergic axon terminals within the medial thalamus from the locus coeruleus. The highest concentration of noradrenergic axons has been reported in the AV, with less dense though still moderate projections to the PV, and reticular nuclei. Furthermore, all ILn receive projections from the LC (Asanuma, 1997; Krout et al, 2002). In addition, it has also been reported that the LC projects to all segments of the MDn (Groenewegen, 1988).

Raphe Nuclei

According to Krout et al (2002), the dorsal raphe nucleus sends projections to all of the ILn thalamic nuclei, whereas the medial raphe nucleus sends moderate projections to only select nuclei, such as the CL, CM and PF nuclei and a light projection to the PC. Vertes et al (1999) indicates this projection from the medial raphe nucleus to the ILn is robust. The dorsal raphe nuclei project to the AV nucleus, with a moderate projection from the dorsal, and a dense projection from the ventrolateral parts (Krout et al, 2002). The PC, and oval paracentral nucleus of the intralaminar nuclei receive input from the rostral, but not the caudal portions of the dorsal raphe nucleus (Krout et al, 2002; Vertes et al, 1999). The median raphe projects most heavily to the lateral segment of MDn, whereas the dorsal raphe is strongly connected with the medial segment of MDn (Groenewegen, 1988).

The Ventral Tegmental Area (VTA) and Substantia nigra (SN)

The ILn and MDn receive projections from the VTA and SN. Both the MDpl and MDl receive non-dopaminergic projections from the VTA and SN pars reticulata (Groenewegen et al, 1990), while the medial segment of MDn and anterior part of the PV also receive projections from the VTA and SN pars reticulata, although these projections are evidently dopaminergic (Groenewegen, 1988). In addition, there are dense projections from the nucleus accumbens core-innervated dorsomedial part of the SN pars reticulata that project to the PC, CeM and medial part of the ventromedial nucleus (Groenewegen et al, 1999).

The Reticular formation

It has been well established that the brainstem reticular formation projects chiefly on all intralaminar thalamic nuclei. The deep mesencephalic reticular nucleus projects to all intralaminar nuclei (Groenewegen, 1988; Krout et al, 2000). In addition, the reticular formation projects to all segments of the MDn (Groenewegen, 1988).

Midbrain / Brainstem Projections to other Key Systems (Limbic, Frontal & Basal Ganglia)

Within the limbic system, noradrenergic input from the locus coeruleus projects prominently to DG and CA3, and lightly to the entorhinal cortex. The VTA projects densely to the rostrolateral portion of entorhinal with terminals in layers I-III. Central and dorsal raphe nuclei terminate in the superficial layers of entorhinal cortex (cited in Amaral & Price, 1995).

The dorsal tegmental nucleus preferentially innervates the lateral mammillary bodies, while the ventral tegmental nucleus preferentially innervates the medial mammillary bodies. There are also sparse serotonergic fibres arising in the dorsal and median nuclei of the raphe that terminate in the medial mammillary bodies. Furthermore very sparse noradrenergic fibres arise in part of the locus coeruleus and end in both lateral and medial mammillary bodies (Swanson, 1987).

There are significant midbrain / brainstem projections from the prelimbic and infralimbic cortical areas. The IL innervations include the substantia nigra pars compacta, periaqueductal gray, parabrachial nucleus and the nucleus of the solitary tract, while the PL innervation includes ventral tegmental area, substantia nigra pars compacta, periaqueductal gray, supralemniscal nucleus, and the dorsal and median raphe nuclei (Vertes, 2004).

A Summary of Midbrain / Brainstem Projections to the Medial Thalamus

As previously mentioned, the midbrain / brainstem projections to the medial thalamus are relatively distinct, with each thalamic nuclei receiving a different set of brainstem inputs with some degree of overlap. The AT receives major cholinergic input from the LDTg and PPTg, with the majority of the LDTg fibres projecting to the AV nucleus. Non-cholinergic input to the anterior group of thalamic nuclei is received mainly from the pretectal nuclei, especially to the LD (Shibata, 1992). Within the MDn, the lateral segment receives cholinergic input from the LDTg, with non-cholinergic inputs to MDn from the median raphe and significant inputs from the substantia nigra. The majority of brainstem input to the ILn is received from the reticular formation, central gray matter, locus coeruleus, parabrachial nucleus, and central tegmental field. There is also cholinergic input from the LDTg and PPTg to the ILn (Hallanger et al, 1987; Krout et al, 2002).

6.6 The Proposed Anatomical Aggregates of Medial Thalamic Nuclei

Based on the above survey of limbic, frontal, basal ganglia and midbrain / brainstem system neural connections associated with the medial thalamus, it appears that there may be at least three distinct aggregates that have relatively similar interconnected links. As indicated in the summary tables clusters of medial thalamic nuclei are connected into common groupings based on their connections to other brain structures. These aggregates are also derived from the Papez circuit (1937), which involves the limbic system structures and from the basal ganglia-thalamocortical circuits described by Alexander et al (1986) and Groenewegen et al (1990; 1999). Of the three aggregates investigated in the current research, one, the anterior (AT) aggregate, is a traditional grouping, while the other two, the lateral (LT) and posteromedial (PT) medial thalamic groupings are non-traditional in the sense that their groupings of medial thalamic nuclei comprise of nuclei from both the ILn and MDn traditional groupings and also midline nuclei.

6.6.1 Anterior Medial Thalamic Region (AT) and Circuit

The principal medial thalamic components include the AV, AM, and AD nuclei. A schematic diagram of the connections of this aggregate is shown in Fig 6 (p. 121). These nuclei have significant neural connections with limbic system structures that include the retro-hippocampal region, in particular the subiculum and pre-and para-subiculum of the hippocampal system, as well as the mammillary bodies, and the cingulate cortices.

6.6.2 Lateral Medial Thalamic Region (LT) and Circuit

The principal medial thalamic components include the central lateral (CL) and paracentral (PC) intralaminar nuclei, and rostral part of the central medial (rCeM) midline nuclei, as well as the lateral (MDl) and paralamellar (MDpl) segments of the mediodorsal nucleus. A schematic diagram of the connections of this aggregate is shown in Fig 7 (p. 123). These nuclei have significant neural connections with the frontal and basal ganglia complex systems that include the dorsal part of the medial prefrontal cortex, the dorsal striatum and the globus pallidus.

6.6.3 Posteromedial Thalamic Region (MT) and Circuit

The principal medial thalamic components include the medial segment (mMDn) and the central segment (cMDn) of the mediodorsal nucleu, and the intermediodorsal (IMD) nucleus. A schematic diagram of the connections of this aggregate are shown in Fig 8 (p.124). These nuclei have significant neural connections with the frontal and basal ganglia complex systems that include the lateral and medial prefrontal cortex, the ventral striatum and nucleus accumbens, the ventral pallidum, and the amygdala.

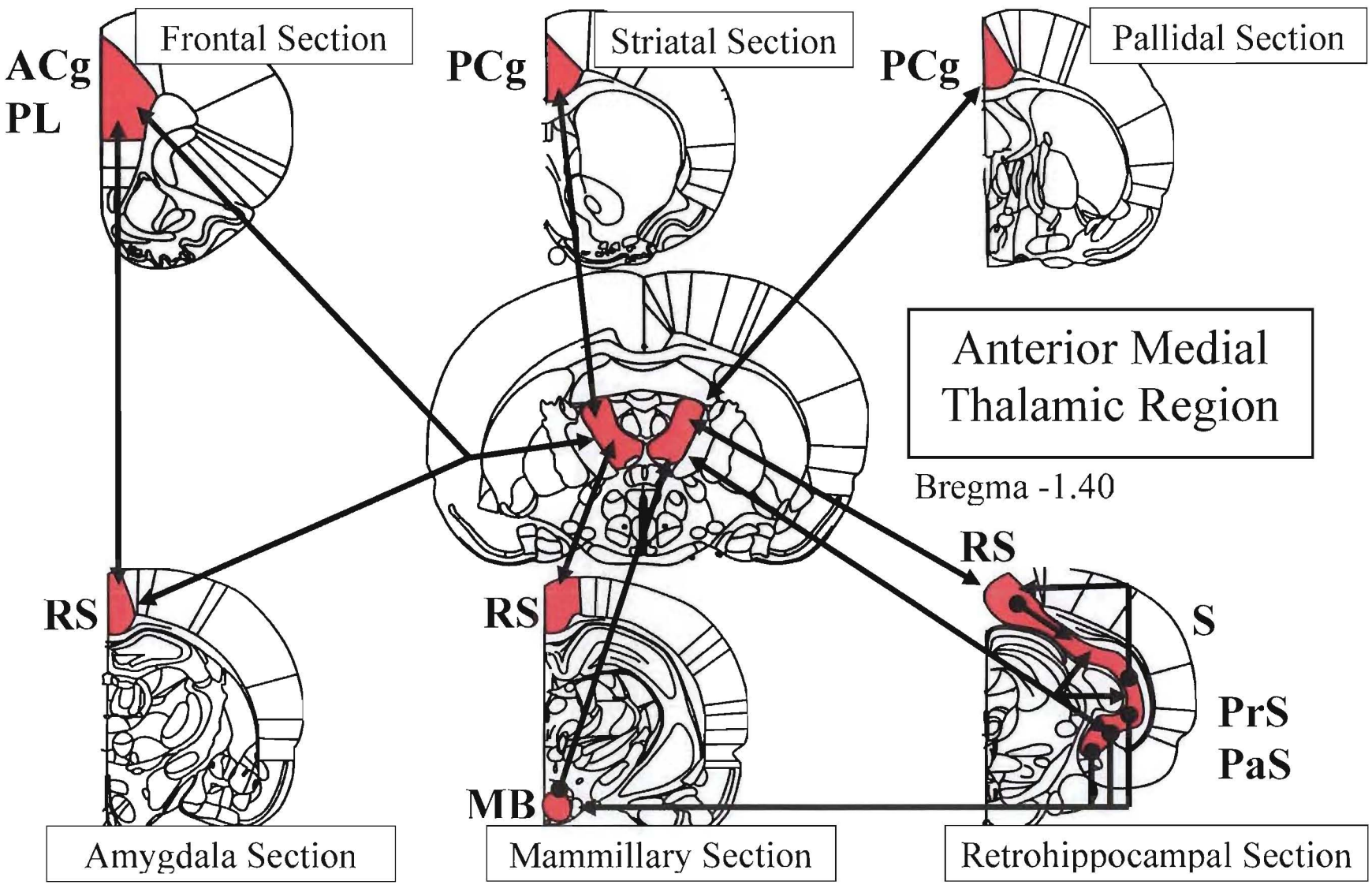

Fig. 6. Schematic diagram illustrating the Prominent Neural Connections of the AT Thalamic Aggregate, shown in the center at Bregma –1.40mm

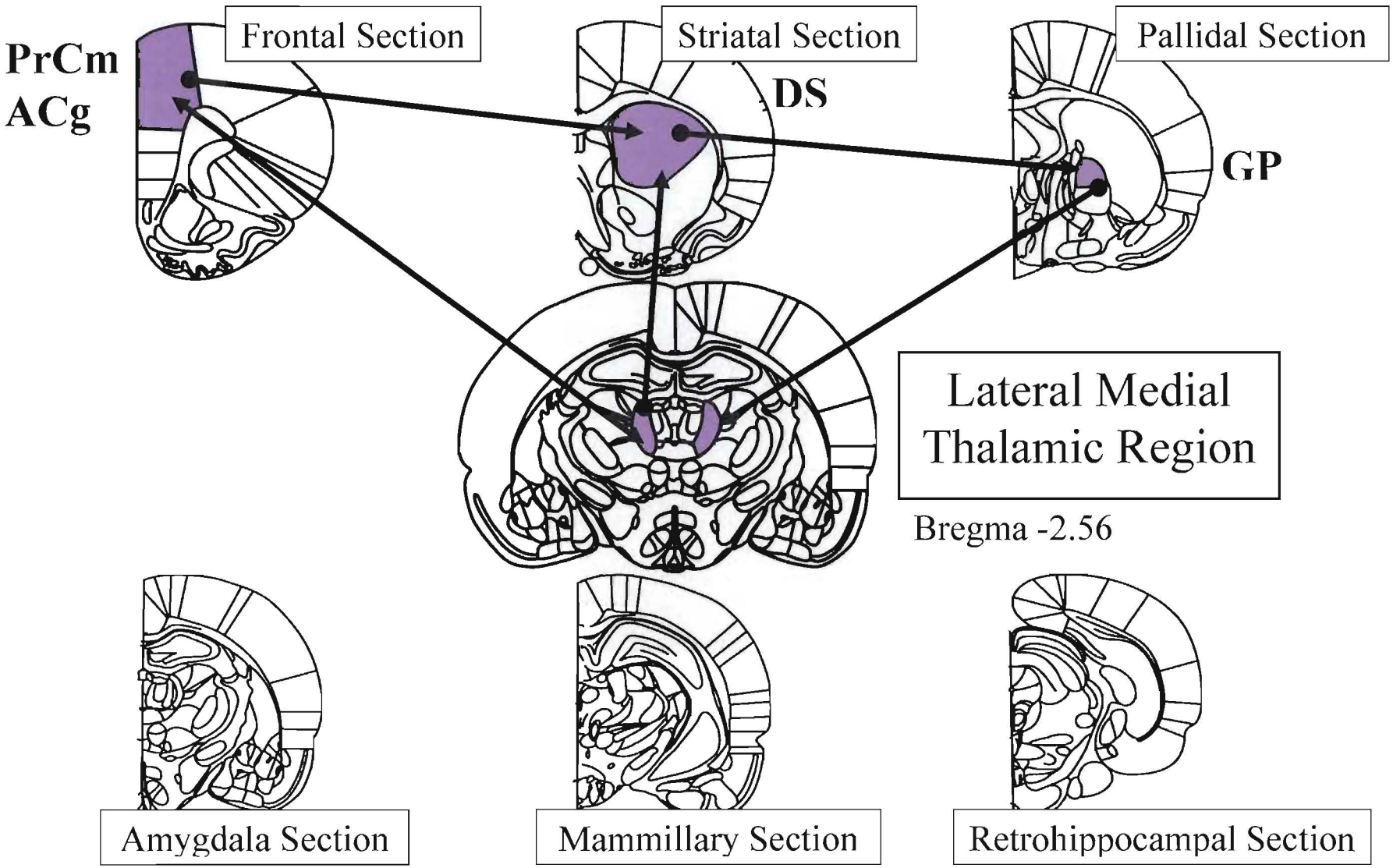

Fig. 7. Schematic diagram illustrating the Prominent Neural Connections of the LT Thalamic Aggregate, shown in the center at Bregma -2.56 mm

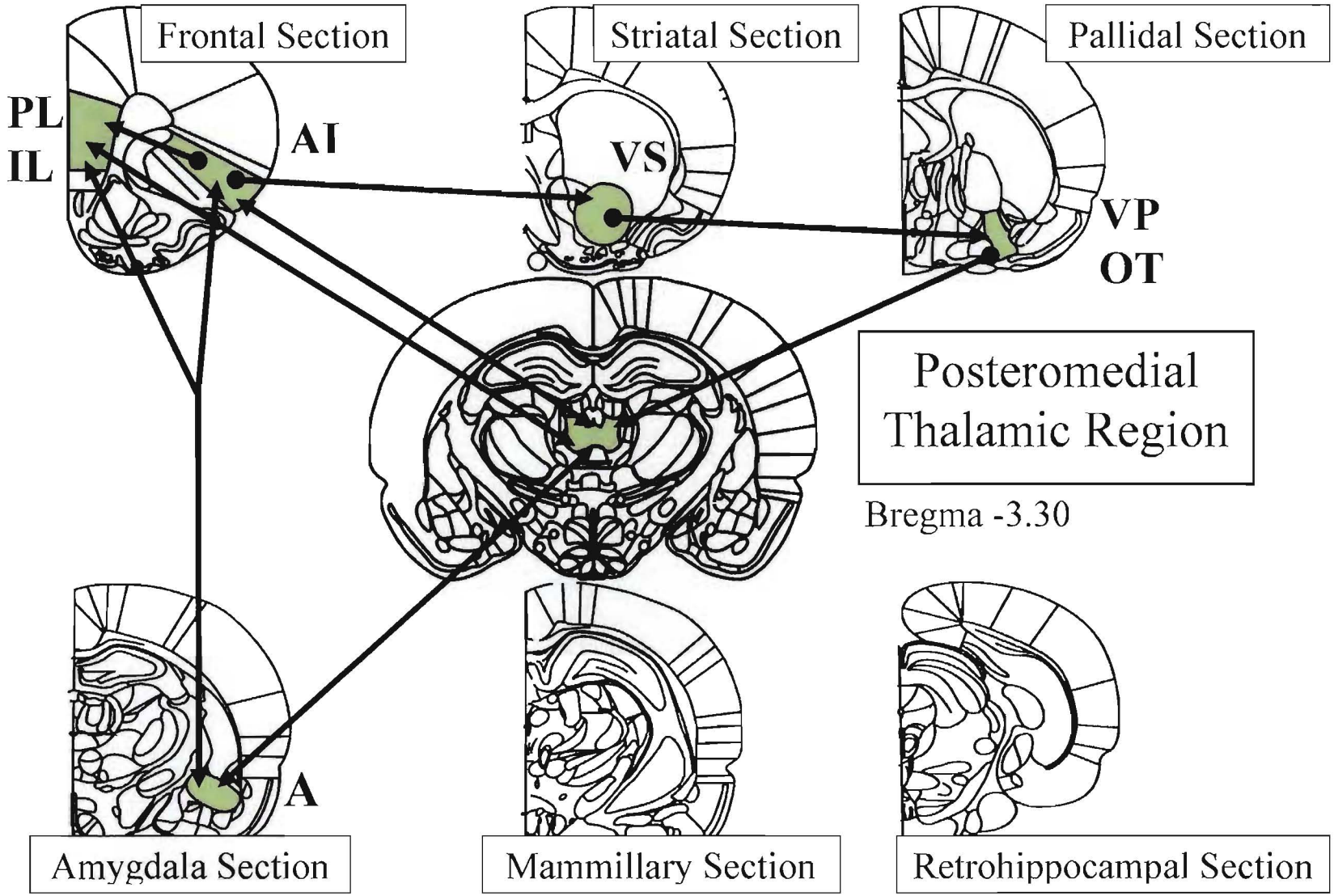

Fig. 8. Schematic diagram illustrating the Prominent Neural Connections of the MT Thalamic Aggregate, shown in the center at Bregma –3.30 mm

Some exclusions to the Aggregates

The laterodorsal thalamic nucleus (LD) was not included in the AT aggregate despite the similarities in several neural connections between the LD and AT. It was not included in the AT aggregate as, for the current research, it was sufficient to assess the functional role of the AT within specific forms of memory. Nevertheless the LD might be included in the AT aggregate, but functional evidence already exists that suggests the LD may not be necessary for the AT deficits produced following lesions. For example, small AT lesions cause spatial memory deficits (Aggleton et al, 1996; Byatt & Dalrymple-Alford, 1996) and there has been reports of limited increase in errors when LD lesion rats are added to the AT lesion impairments (Warburton et al, 1997; van Groen et al, 2002).

The caudal CeM was not included in either the LT aggregate or MT aggregate, as the significant projections of this region are to the primary motor, gustatory, visceral and primary somatosensory cortices. Additionally, a recent review of van der Werf et al (2002) suggests this region have commonalities with the rhomboid nucleus.

Only the midline IMD nucleus was included in the MT aggregate because of its selective projections to the ventral striatum, lateral and medial PFC and amygdala. The IMD projections are in some ways similar to those of the PV and PT, but these regions have more diffuse projections too, which include the hippocampus and this led to their exclusion.

There may also exist other significant interconnections not yet documented. Therefore these current AT, LT and MT aggregates must remain in fluid form. In addition, further groupings of similarly connected thalamic nuclei may exist. However, any possibility for further groupings was not investigated in the current thesis.

6.7 Functional Implications of these Circuits to Memory

The concept of multiple memory systems in the brain working in parallel has been recognised for many years now (Sherry & Schacter, 1987; Gaffan et al, 1993; Kesner & DiMattia, 1987; Kesner et al, 1993; McDonald & White, 1993; 2002; Scoville & Milner, 1957, 2000; Squire & Zola-Morgan, 1991). Nonetheless, the theories related to multiple memory system do not appear to fully recognise the functional contributions made by the medial thalamic nuclei to information processing conducted by these independent neural circuits. Yet the neuroanatomical evidence suggests there are significant links between these regions and the medial thalamus.

The AT Aggregate and A Hippocampal System Circuit

It is well recognised that the interactions between the medial temporal lobe structures and the medial diencephalon are involved in anterograde amnesia in humans (Aggleton & Sahgal, 1993; Eichenbaum & Cohen, 2001; Squire & Knowlton, 1995; Squire & Zola-Morgan, 1991) and spatial (episodic-like) memory processing in rodents (Aggleton & Brown, 1999).

Within animal studies, a substantial body of research has implicated the hippocampus, and its major output structure, the fornix in spatial memory processing. Hippocampal lesions (Jarrard, 1993; White & McDonald, 1993) and fornix lesions (Olton & Papas, 1979) impair performance in the 8-arm radial maze. Similarly, hippocampal lesions (Morris et al, 1982; Sutherland et al, 1982; Sutherland et al, 1983; DiMattia & Kesner, 1987) and fornix lesions (Nilsson et al, 1987; Sutherland & Rodriguez, 1989; McDonald & White, 1994) disrupt both the acquisition and retention of place learning for a hidden platform version of the standard water maze task. Additionally, the extensive work of Kesner and colleagues (Gilbert et al, 1998; Kesner & DiMattia, 1987; Kesner, 1998; Lee & Kesner, 2002, 2003) involving a variety of memory tasks have provided evidence for the specific functioning of the hippocampus in spatial (and temporal) information processing.

More recent animal lesion models have provided evidence that the other connected brain structures of the extended hippocampal system also contribute to spatial memory processing. Mammillary bodies lesions (e.g. Sziklas & Petrides, 1999; Santin et al, 1999; Vann & Aggleton, 2003) and retrosplenial cortex lesions (Vann & Aggleton, 2003; Vann et al, 2003) impair performance in the radial maze, T-maze, and water maze tasks. An analysis of the effects of anterior thalamic lesions in memory processing has already been discussed in this thesis and a comprehensive table of behavioural studies was included in Chapter 5.

All of this evidence indicates that lesions to the interconnected structures of the extended hippocampal system impair the processing of information about the spatial relationships amongst the available environmental cues (Aggleton & Brown, 1999; Gaffan & Parker, 2000).

The LT Aggregate and The Dorsal Frontal Cortex/ Dorsal Striatum Circuit

It has been proposed that the dorsal striatum is the central structure within a parallel multiple memory system involved in stimulus-response learning and memory processing. That is, simple discrimination tasks, in which a reinforcer repeatedly follows a response made in the presence of a stimulus, are instances of stimulus-response learning attributed to the dorsal striatum system (McDonald & White, 2002).

Animal lesion models have further confirmed the specific contribution to stimulus-response learning made by the dorsal striatum. Dorsal striatum lesions impaired response-dependent egocentric response tasks in a radial arm maze but not response-dependent tasks based on spatial cues (Cook & Kesner, 1988). Packard and McGaugh (1996) reported dissociation between dorsal striatum and fimbria-fornix lesions in a water maze, using different tasks relying on either egocentric (local cues) or on spatial cues. McDonald and White (1993) reported dissociation between dorsal striatum and hippocampus lesions in performance of a win-stay (stimulus-response processing task) and a win-shift (spatial cue processing task) in the radial maze. All of this evidence suggests that an intact dorsal striatum is necessary for the acquisition and maintenance of simple stimulus-response tasks and is consistent with the hypothesis that the hippocampus and dorsal striatum function independently of each other.

Animal lesion studies investigating the functions of the dorsal region of the medial prefrontal cortex have also reported similar deficits to those related to lesions involving the dorsal striatum. These studies are also suggestive about the importance of the neuroanatomical interconnections between the dorsal striatum and the dorsal part of the medial prefrontal cortex. Recent reviews (Kesner, 2000; Uylings et al, 2003) of behavioural studies of prefrontal cortex functioning in rats suggests that in the rat, the dorsal prefrontal cortex, that is the anterior cingulate and the medial precentral cortical areas, participate in processing working memory for motor responses, in memory for requiring temporal processing of information and in paired associate learning. Lesions to the anterior cingulate and medial precentral cortical areas impair memory for egocentric turn responses (Ragozzino & Kesner, 2001), but these lesions do not disrupt performance in spatial processing or visual discrimination or configurations of object-place learning (Kesner & Ragozzino, 2003).

Animal lesion work investigating the functions of the medial thalamus that form the additional link in the circuit that connects these dorsal striatum and dorsal prefrontal cortex regions is relatively non-existent. Although more extensive intralaminar thalamic nuclei lesions have been assessed and the details of performance on behavioural tasks is provided in Chapter 5, this evidence remains relatively inconclusive because of the extensive overlap in brain injury sustained to either or both the AT or MDn thalamic nuclei.

The MT Aggregate and The Amygdala / Ventral Striatum / Prefrontal Cortex Circuit

It has been proposed the amygdala is the central structure in another parallel, independent multiple memory system involved in stimulus-reinforcement memory. That is, the stimulus

properties of a reinforcer and a neutral stimulus form an association that results in the ability of the stimulus to elicit an array of responses normally produced by the reinforcer (McDonald & White, 2002). It is proposed that this type of memory is similar in some ways to the Pavlovian or Classical conditioning originally described by Pavlov (1927). Lesions of the amygdala should impair conditioning based on responses normally elicited by reinforcers according to the model proposed by White & McDonald (2002).

In studies using monkeys, it has been suggested that the amygdala mediate the affective aspects of memory, as in the association of stimuli with rewards and punishments (Spiegler & Mishkin, 1981; Gaffan, 1994; Gaffan et al, 1993) and the consolidation of memories gained by emotional contexts (Packard et al, 1994; Cahill et al, 1995). Furthermore, human patients with selective damage to the amygdala show impairments in face recognition and difficulties with affective prosody (Adolphs et al, 2000; Adolphs & Tranel, 2003, 2004).

Analysis of MDn lesions and performance in behavioural and memory tasks conducted in previous research work with animals has been discussed previously in this thesis and a detailed table of behavioural studies is included in Chapter 5.

6.8 The Three Medial Thalamic Aggregates and Memory

Brain damage in the medial thalamus, due to localized injury or the alcoholic Korsakoff syndrome, is associated with dense amnesia in humans. Attempts to model a critical lesion locus for these deficits have frequently emphasised one of three thalamic structures, either the AT, the ILn / IML, or the MDn but the neural basis of thalamic amnesia remains elusive.

An alternative view is that the various medial thalamic regions each support different learning and memory processes. This proposal is based on the previous survey detailed in this chapter of the prominent neural connections of the medial thalamic nuclei, each forming components in multiple memory systems.

It now remains for the current proposals of medial thalamic involvement in different neural circuits responsible for different attributes of memory to be tested. Several experiments were conducted to assess the effects of performance in various memory tasks following lesions to the AT, LT and MT thalamic aggregates (details in Chapters 7 – 9).

Chapter 7

Medial Thalamic Involvement in Specific Attributes of Memory

This chapter documents the first of three different experiments (other experiments are documented in Chapters 8 and 9) that was conducted to assess memory impairments following lesions to each of the different aggregates of medial thalamic nuclei that were proposed in the connections overview (Chapter 6). In the current experiment rats were tested across four behavioural tasks that assess different attributes of memory, namely memory for spatial location, memory for reward value, memory for temporal order and memory for familiarity versus novelty object recognition. This experiment was conducted in order to assess the proposal that the each of the different aggregates of the medial thalamic nuclei (AT, LT and MT) are involved in specific attributes of memory.

7.1 General Introduction

Attempts to model a critical lesion locus for thalamic amnesia in animals have frequently emphasised one of three thalamic structures, either the anterior thalamic (AT) nuclei (Aggleton & Brown, 1999; Byatt & Dalrymple-Alford, 1996), the intralaminar nuclei (ILn) / internal medullary lamina (IML) / midline (Burk & Mair, 1998; Young, Stevens, Converse, & Mair, 1996) or the mediodorsal thalamic (MDn) nuclei (Gaffan & Parker, 2000; Stokes & Best, 1988). However to date, in the animal models the conclusions remain elusive, that is, as indicated in Chapter 5, the lesions induced to any one of these groupings of thalamic nuclei have been unable to account for the broad range of memory and other deficits associated with thalamic amnesics cases in humans.

An alternative view, and the one that is proposed for this thesis, is that the various medial thalamic regions each differentially support specific learning and memory processes. As was indicated in Chapter 6, the prominent neural connections of the medial thalamic nuclei suggest that at least three nuclear aggregates are each involved in separate memory systems. Briefly, the anterior thalamic nuclei (AT) are characterised most prominently by interconnections with the retro-hippocampal region, especially

pre- and para-subiculum, the posterior cingulate / retrosplenial cortex (Shibata, 1993, 1998; van Groen, Kadish, & Wyss, 1999; van Groen & Wyss, 1990; Van Groen & Wyss, 1995), and input from the mammillary bodies (Shibata, 1992). The lateral thalamic region (LT) have common connections in a circuit that includes the anterior cingulate and precentral cortical areas of rat prefrontal cortex (PFC), as well as dorsal striatum and globus pallidus of the basal ganglia (Berendse & Groenewegen, 1991; Groenewegen & Berendse, 1994; Van der Werf, Witter, & Groenewegen, 2002; Vertes, 2002). The posteromedial thalamic region (MT) is most prominently connected are with the amygdala, ventral striatum, ventral PFC and agranular insular cortex (Groenewegen, 1988; Groenewegen, Berendse, Wolters, & Lohman, 1990).

This current group of experiments comprises for the first time, an evaluation of the comparative behavioural effects of selective lesions to these three medial thalamic aggregates (as confirmed by extensive searches of the previous research literature). The AT's connections make it highly likely that this region is an integral component of the brain's spatial memory system (Aggleton & Brown, 1999; Aggleton & Sahgal, 1993). A radial maze task was used to test allocentric spatial memory, which is widely regarded as an analogous test for episodic-like declarative memory processing in rats (Aggleton & Pearce, 2001). Previous evidence is consistent with the prediction that selective AT damage impairs spatial memory (Byatt & Dalrymple-Alford, 1996; Moran & Dalrymple-Alford, 2003; Sziklas & Petrides, 1999; van Groen, Kadish, & Michael Wyss, 2002) but lesions that include the LT or MT regions have also been reported to affect spatial memory (Alexinsky, 2001; Burk & Mair, 1998; Hunt & Aggleton, 1998; Stokes & Best, 1988; Young et al., 1996). The second task assessed event memory for the temporal order of two familiar objects (Mitchell & Laiacona, 1998). Both the medial PFC and the hippocampal system may play a role in memory that requires the processing of temporal information (Kesner, 1998; Kesner, 2000), so it is possible that all three thalamic regions affect memory for temporal order. The third task assessed recognition memory for familiar versus novel objects, which may require normal functioning of the mediodorsal thalamic nucleus (Aggleton & Brown, 1999). Finally, both the agranular insular PFC and amygdala have been implicated in memory for reward value, that is, memory for affective information, but not spatial memory (DeCoteau et al, 1997; Kesner & Williams, 1995; Ragozzino & Kesner, 1999). It was therefore predicted that only MT lesions, with their significant neural connections with these brain regions, would impair performance in a reward magnitude task.

7.2 Materials and Method

7.2.1 Subjects

The experiment used female hooded rats weighing between 180 and 220 gm at the beginning of the experiments. Throughout the research, rats were housed together in groups of four under a reversed light schedule (off 0800-2000 hrs). Rats had free access to water and were maintained at 80-85% of ad-libitum weight, bar free food access just prior to and after surgery to facilitate postoperative recovery. Testing occurred between 0830 and 1930 hr at a rate of 5-6 daily sessions per week. All protocols conformed to the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Animal Ethics Committee of the University of Canterbury.

7.2.2 General Surgery Procedure

Anesthetized rats (50 mg/ml pentobaribitone at 1.65 ml/kg, 20 minute after 0.130 mg/ml atropine at 1.5 ml/kg, ip) were placed in a stereotaxic apparatus (David Kopf Instruments, Tujunga), with the incisor bar set 7.5 mm below the interaural line rather than a more traditional orientation. This non-traditional angle was adopted to minimize or avoid fornix damage; the fornix is a band of fibres that overlies the thalamus and one of its primary connections is between the hippocampus, the mammillary bodies and anterior thalamus.

The exact locations and volumes for the lesions to the target regions in the medial thalamus were determined using a number of pilot surgeries prior to the research commencing. This conscientiousness has led to one of the advantages of the current research, that is the lesions to the target regions are highly selective, having caused very minimal damage to the other closely located regions of interest. The neurotoxic lesion dissolved in phosphate buffered saline pH 7.20 at a concentration of 0.12 M NDMA (Sigma Chemicals, Australia) was infused using a 1-μl Hamilton syringe driven by a motorized infusion pump.

All stereotaxic coordinates were calculated from bregma and were adapted from the stereotaxic atlas of Paxinos and Watson (1998). For accuracy, it was necessary to use AP coordinates in the horizontal plane that varied according to the Bregma to Lambda (B-L) distance in each individual rat. All AP coordinates are relative to bregma. Table 7 details these BL measurements and corresponding AP coordinates, as well as the ML

and DV coordinates and infusion volumes used in the present study. Further detail is included in the following text.

Table 7. Lesion coordinates for individual rat Bregma–Lambda (B-L) measurements and corresponding AP coordinates, as well as ML and DV coordinates, and NMDA Infusion Volumes for the Three Medial Thalamic Aggregates Assessed in the Present Study

	AT		LT			MT	
	Ant	Post	Two Ant Sites		Post	Ant	Post
B-L distance for AP coordinates							
0.60-0.61 cm	-0.245	-0.255	-0.345		-0.385	0.365	-0.405
0.62-0.63 cm	-0.255	-0.265	-0.355		-0.395	-0.375	-0.415
0.64-0.66 cm	-0.265	-0.275	-0.365		-0.405	-0.385	-0.425
0.67-0.68 cm	-0.275	-0.285	-0.375		-0.415	-0.395	-0.435
ML	±0.120	±0.146	±0.130		±0.130	0.0	0.0
DV	-0.580	-0.556	-0.60	-0.56	-0.56	-0.560	-0.570
Volume μl	0.12	0.12	0.08	0.06	0.06	0.20	0.18

Abbreviations: Ant = anterior AP site, AP = anterior-posterior direction from bregma, AT = anterior thalamic lesion, DV = dorsal-ventral direction from dura, LT = lateral medial thalamic lesion, ML = medial-lateral direction from midline, Post = posterior AP site; PT = posteromedial thalamic lesion.

For AT lesions, AP coordinates at the anterior site thus ranged from –0.245 to –0.275 cm, ±0.120 cm lateral to the midline (ML), and –0.58 cm ventral from dura (DV). At the posterior AT site, AP ranged from –0.255 to –0.285 cm, and was ±0.146 cm ML and –0.556 cm DV. The volume of NMDA at each AT site was 0.12 μl infused over 4 min. For all infusions the syringe remained in situ for a further 3 min dispersion. For the LT lesions, AP at the anterior site was –0.345 to –0.375 cm, at ±0.130 cm ML, and a volume of 0.08 μl of NMDA was infused over 2 min at –0.56 cm DV followed by 0.06 μl for 2 min at –0.60 cm DV. The AP at the posterior LT site was –0.385 to –0.415 cm and was ±0.130 cm ML, with 0.06 μl NMDA infused for 2 min at –0.56 cm DV only.

For MT lesions, AP at the anterior site was –0.365 to –0.395 cm, centered at midline, and 0.18 μl NMDA was infused over 4 min at –0.560 cm DV. At the posterior MT site, AP was –0.405 to –0.435 cm, again centered at the midline, with 0.20 μl NMDA infused over 4 min at –0.570 cm DV. Sham lesion controls also received surgery but no infusion; the same AP and ML coordinates were used from the three lesion groups, spread evenly across control rats, at –0.25 cm DV at the corresponding sites.

7.2.3 General Histology Procedure

After completion of all experiments, rats were intracardially perfused (0.9% saline followed by 4% formalin) and brains were fixed in 4% formalin for at least 24 hr before transfer to long-term glucose solution. Frozen coronal sections throughout the thalamus were cut at 50 μm and sections stained with cresyl violet. Verification of thalamic damage was made by estimating lesion size using the relevant plates from a standard atlas (Paxinos and Watson, 1998) and expressed as a percent of the volume of the intact region using distances provided in the atlas.

7.3 Spatial Working and Reference Memory Processing

7.3.1 Apparatus

Rats were trained on an elevated (85 cm above floor) 12-arm radial maze, with a 35 cm wide central wooden hub painted black and equally spaced aluminum arms (9 cm x 65 cm). Each arm had 3 cm high borders and a single Perspex barrier (25 cm high x 20 cm) adjacent to the hub. A black wooden insert (8.5 cm x 5 cm wide, x 3 cm high) at the end of each arm incorporated a food well (2 cm diameter, 1 cm deep). The wells were baited with 2 x 0.1 gm pieces of chocolate; inaccessible chocolate was present at all times below the wells. Clear Perspex guillotine doors that could be raised singly or as one unit governed access to each arm.

7.3.2 Procedure

Before surgery, rats received familiarisation and training on one of three different configurations of 8 baited / 2 never-baited arms, randomised across rats (all 12 arms were used across the twelve configurations: see Appendix A for configurations). The maze was always wiped clean with a weak detergent solution between rats. A 5s confinement to the central hub between arm choices was used to minimise the adoption

of any simple response strategies during the first 25 sessions and then training continued to the preoperative criterion of no more than an average of 1 reference memory errors across three consecutive sessions (75% correct or better; about 90 sessions); preoperatively, working memory errors occurred infrequently. Rats were matched for accuracy in avoiding the never-baited arms and randomly assigned to one of the four lesion groups. Following 10 days of postoperative recovery, retesting in the 8 baited / 2 never-baited radial maze task continued for 15 sessions.

7.4 Memory for Temporal Order of Presented Objects

7.4.1 Apparatus and Procedure

This task involved objects being placed in a small box (36 cm wide x 63 cm long x 34 cm high), with ample sawdust covering the floor. One of the longer walls of the box was made of clear Perspex and the remaining walls and floor were wooden painted gray. An infrared camera mounted above the box relayed recorded images to the adjacent control room. The objects used in this task were triplicates of a weighted glass bottle (210 cm high) and aluminium can (130 cm high). When present, an object was centred 1 cm away from a midway point along each short-end wall so that rats could not circle them. The light level in all testing rooms was set at 34 lux. Immediately after postoperative radial maze testing, single rats were familiarised in the empty box, being started in the centre of the box facing the longer wooden wall. Rats received four daily 1-hr familiarisation sessions, followed on the fifth day by a procedural familiarisation session of 5-min, 1-hr in a clean opaque-covered holding cage located in the test room, and a further 5-min back in the empty box. On the next day, the rat received a 5-min study trial to explore a pair of identical objects (A), followed 1-hr later by a second 5-min study trial to explore a second pair of identical objects (B; order of objects counterbalanced across rats; see Fig. 9). The rat was placed in the holding cage during the 1-hr interval. On completion of the second study trial, the rat was placed in the same holding cage for another 1-hr delay, after which the test trial began. For the test trail, the rat was placed back in the box for 5-min, with a triplicate of object A and a triplicate of object B (positions counterbalanced across rats). The time spent exploring each object was recorded when the rat was 2 cm or closer and facing the object (climbing not counted).

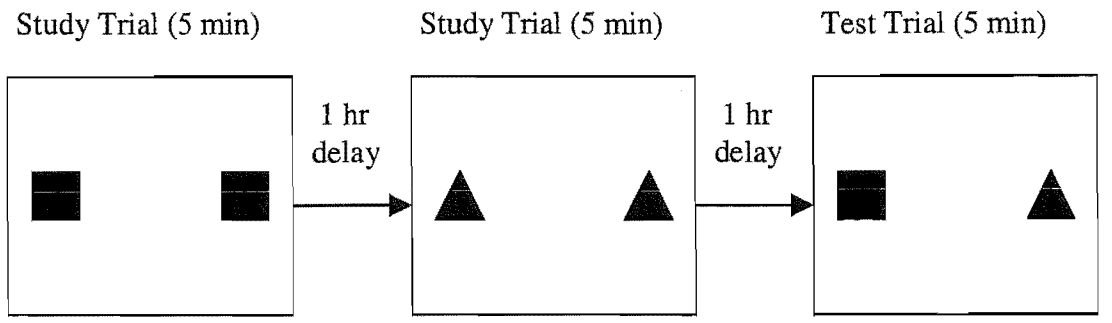

Fig. 9. Schematic diagram showing the procedural method for the task that assessed memory for temporal order of two familiar objects.

7.5 Memory for Familiarity versus Novelty Object Recognition

7.5.1 Apparatus and Procedure

Rats received the spontaneous object recognition task in the same boxes 48 hr after the test trial for temporal order memory. Individual rats were given a 5-min study trial to explore a pair of identical objects (C) before being placed in separate holding cages for a 2-hr delay prior to the object recognition test (see Fig. 10). In the test trial, individual rats were returned to the box for 5-min to explore a triplicate of object C and a novel object (D). The two objects, a weighted plastic bottle (170 cm high) and a conical light bulb (110 cm high), were counterbalanced across study and test trials. The time spent exploring each object was recorded when the rat was 2 cm or closer and facing the object (climbing not counted).

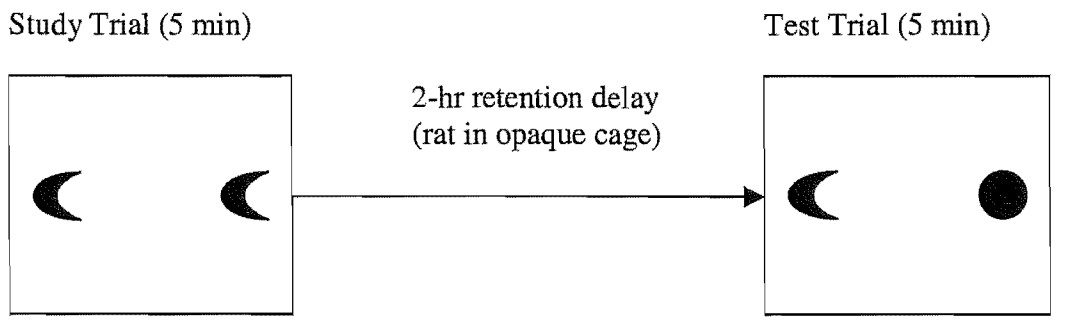

Fig. 10. Schematic diagram showing the procedural method for the task that assessed recognition memory for novelty versus familiarity of objects.

7.6 Acquisition of Reward Magnitude Task

7.6.1 Apparatus and Procedure

The apparatus and procedure was modelled on that described by Kesner (Kesner & Williams, 1995). The task was conducted using a small wooden platform painted black, divided into two halves by a black wooden door operated by a pulley system. Each end of the platform contained a central food well, covered by small objects (weighted plastic bottles, 120-150 cm high). A red Plexiglas sheet extended across one side of the table to block the rat's view of the experimenter and the room but allow access to either end of the platform to replenish food wells; the opposite side of the platform was against a gray wall. Rats received familiarization to the reward magnitude apparatus at a break mid-way through pre-surgery radial maze training. They were shaped to displace the object that covered the food well and were habituated to three brand cereals: Maximise (20% sugar) and Froot Loops (40% sugar), the reward-value discriminative stimuli, and Cocoa Pops (40% sugar), the additional food reward. Immediately after recognition memory for novelty versus familiarity testing (i.e. postoperatively), rats were given a brief re-familiarization to the apparatus before acquisition training begun using a go/ no-go procedure. In each session, rats received 12 trials (6 positive and 6 negative trials) using randomisation sequences (Fellows, 1967). On one side of the platform per trial, rats ate either a ½ piece of Maximise (20% sugar) or a ½ piece of Froot Loops (40% sugar), which served as the discriminative stimulus for either an additional reward (Cocoa Pops) or no reward (counterbalanced across rats) in the food well on the opposite side (following a minimum delay of 2-4s controlled by the central door). Rats were given a maximum of 10s to dislodge the object before the next trail began. Latency to cross the platform on negative and positive trials was the dependent measure. Post-operative training was conducted until 24 sessions were completed, then following a four-week break further sessions were conducted to assess retention and reacquisition of the reward-value association.

7.7 Data Analysis

In task one, the spatial memory task, differences between the lesion groups were assessed using repeated-measures analysis of variance (ANOVA) for number of errors made (working and reference) and the number of arm visits before an error during daily testing in the radial arm maze averaged across blocks of three sessions. One-way ANOVA and repeated measures ANOVA were used to assess differences across choice

latency to correct and incorrect working memory and reference memory arm visits. In tasks two and three, the temporal order memory and familiarity versus novelty object recognition task, between-groups ANOVA and independent single sample t-test against a mean of zero were used to assess the level of preference for the objects and assess differences between the lesion groups. In task four, the reward magnitude task, a between-groups ANOVA was used to assess latency to cross the platform during acquisition and later retention / re-acquisition of the memory for reward magnitude task. Correlational analyses including all rats with medial thalamic lesions (N= 36; i.e. including those rats with a lesion to the AT, LT and MT that were excluded from the between-group behavioural analyses, but not controls) and number of errors in the radial maze task, ratios for temporal order and object recognition, and days to criterion on the reward magnitude task were assessed.

7.8 Results

7.8.1 Histology

The minimum and maximum extent of successful lesions is shown in Fig. 11 (p. 138). Successful lesions met the criteria of at least 50% damage to the intended aggregate and less than 50% damage to either of the alternate aggregates. These criteria ensured that damage was relatively large in the target regions and unintended damage to other thalamic structures was relatively minor in all successful lesions (Table 9 on p. 139). Two independent raters evaluated the lesion damage in the medial thalamus for this experiment and the two subsequent experiments (myself and then John Dalrymple-Alford) and any discrepancies were clarified by mutual agreement. That is, we can be reasonably confident in the accuracy of the lesion summaries presented. Three AT lesion rats were excluded due to additional substantial damage to the LT and MT regions (all poor in the spatial memory task, ranked 1st, 2nd and 7th worst of the 47 rats in total, while in the reward magnitude task these rats were ranked 1st equal, 13th equal and 20th equal worst). Two LT lesion rats were excluded, one due to additional unilateral AT damage (poor on the spatial memory task, ranked 13th worst, just below the 12 AT lesion rats), while the other rat had additional extensive damage in the MT (poor on the reward magnitude task, ranked 1st equal-worst). Two MT animals were excluded because neither received sufficient damage to the intended aggregate (both performed similar to controls on all tasks).

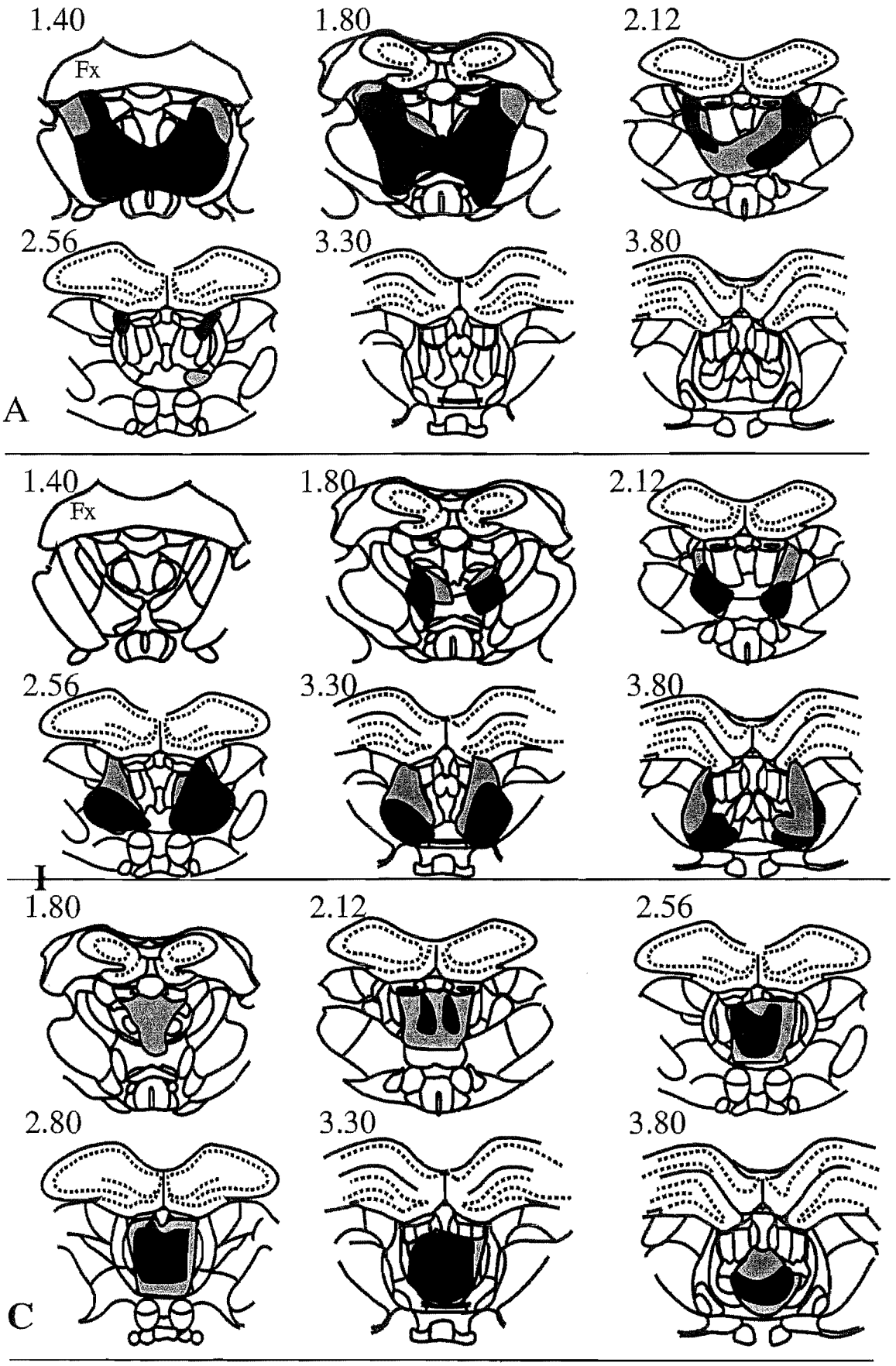

Fig. 11. A series of coronal sections throughout the medial thalamus showing the area of cell loss with the smallest (*black*) and largest (*gray*) thalamic lesions. A: Anterior thalamic rats (AT). B: Lateral thalamic rats (LT). C: Posteromedial thalamic rats (MT). Coronal sections are adapted from Paxinos and Watson (1998) and coordinates are mm from bregma.

Table 9. Median (Range) of Bilateral Damage to the AT, LT and MT Medial Thalamic Aggregates and Adjacent Medial Thalamic Nuclei following micro-infusion of NMDA.

Region	AD	AM	AV	Total AT%	CL	MDl/ MDpl	PC	rCeM	Total LT%	IMD	MDc	MDm	Total MT%	IAM	LD	PT	PVA	PV/ PVP	Re/ Rh
Group																			
AT n= 9	99.8 (81.8-99.8)	97.6 (87.1-100)	83.4 (44.1-100)	91.2 (75.9-96.3)	13.6 (6.6-30.6)	7.7 (0.0-100)	31.0 (23.5-47.5)	53.8 (26.0-99.9)	22.8 (15.1-45.9)	0.0 (0.0-38.7)	0.1 (0.0-47.2)	4.8 (0.3-40.9)	5.8 (2.0-44.0)	84.1 (62.0-100)	3.0 (0.3-9.3)	33.6 (19.4-60.0)	2.6 (0.4-22.5)	0.0 (0.0-1.7)	0.9 (0.0-71.9)
LT n=10	0.0 (0.0-24.0)	2.3 (0.0-19.6)	0.4 (0.0-10.9)	1.1 (0.0-10.5)	80.9 (70.4-96.7)	71.7 (47.6-100)	70.8 (63.5-78.8)	20.9 (5.3-24.6)	65.6 (63.2-79.8)	0.0 (0.0-8.1)	36.6 (11.7-85.4)	20.1 (16.7-43.1)	20.2 (13.0-43.0)	0.1 (0.0-5.3)	0.5 (0.0-9.1)	0.0 (0.0-2.8)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 0.0-1.3)
MT n=10	0.0 (0.0-24.0)	0.0 (0.0-19.6)	0.0 (0.0-0.0)	0.0 (0.0-2.4)	0.0 (0.0-1.6)	0.3 (0.0-14.2)	5.5 (0.0-13.4)	13.4 (2.2-76.7)	5.5 (1.0-17.1)	99.7 (69.6-100)	63.8 (41.8-94.7)	78.5 (63.4-93.0)	71.1 (56.1-89.8)	0.0 (0.0-38.6)	0.0 (0.0-0.0)	0.0 (0.0-22.8)	1.6 (0.0-66.1)	62.0 (10.0-100)	0.0 (0.0-0.6)

Abbreviations:
AD= anterodorsal nucleus; AM= anteromedial nucleus; AV= anteroventral nucleus; CL= centrolateral nucleus; IAM= interanteromedial nucleus; IMD= intermediodorsal nucleus; LD= laterodorsal nucleus; MDc= central segment of mediodorsal nucleus; MDl= lateral segment of mediodorsal nucleus; MDm= medial segment of mediodorsal nucleus; MDpl= paralamellar segment of mediodorsal nucleus; PC= paracentral nucleus; PT= parataenial nucleus; PV/ PVP= paraventricular nucleus/ posterior paraventricular nucleus; PVA= anterior paraventricular nucleus; rCeM= rostral region of central medial nucleus (Van der Werf et al, 2002); Re/ Rh= reunions nucleus/ rhomboid nucleus; Total AT%= total percent damage to anterior medial thalamic target; Total LT%= total percent damage to lateral medial thalamic target; Total MT%= total percent damage to posteromedial thalamic target.

7.8.2 Spatial Memory

Rats were trained preoperatively in the 12-arm radial maze and then matched groups were retested postoperatively. The AT lesion group showed marked impairments in spatial memory that persisted throughout the period of postoperative testing. In contrast, rats with LT or MT lesions were comparable to controls. As shown in Fig. 12, AT rats consistently made about 7 or 8 re-entries per trial to the 8 baited arms (working memory errors), whereas LT, MT and Control groups showed equally accurate performance with very few such re-entries and analysis confirmed there was a significant effect of lesion, ($F_{3,36}$ = 186.11; $p < 0.0001$). While there was an overall improvement over blocks of 3 sessions, ($F_{4,144} = 4.38$; $p < 0.003$), and a slight reduction in errors in the AT group at the end of testing, the lesion x block interaction was negligible ($F < 1.0$).

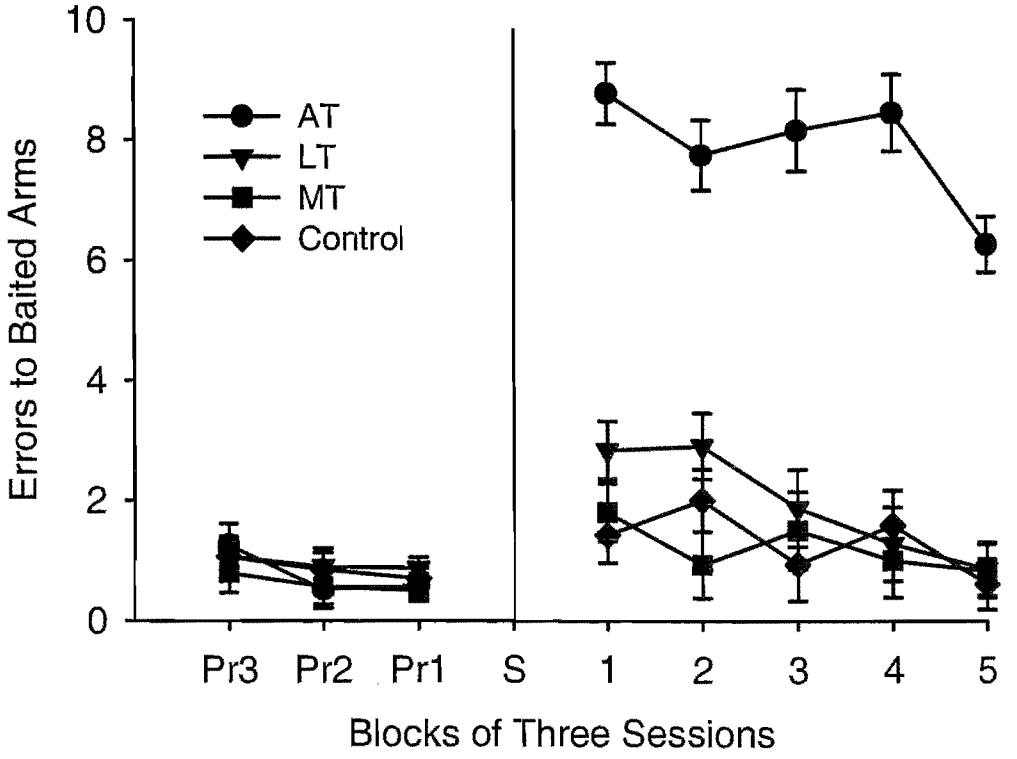

Fig. 12. Spatial Memory: mean (±SEM) number of errors to baited arms (working memory errors) for all groups, pre- and post-operatively in the radial arm maze, separated into blocks of three sessions. Pr3, Pr2, Pr1 = last three blocks of pre-operative sessions, S = surgery

Analysis of reference memory errors (initial visits to the 2 never-baited arms, Fig. 13, p. 141) revealed a similar pattern across groups with a significant lesion effect, ($F_{3,36}$ = 10.63; $p < 0.0001$) and block effect, ($F_{4,144} = 4.24$; $p < 0.003$) but no lesion x block interaction, ($F < 1.0$). The AT group made an average 1.38 (SD= 0.25) entries to never-

baited arms across blocks of sessions compared with LT = 0.83 (0.29), MT = 0.64 (0.20), and Control = 0.78 (0.41) groups. Analysis of re-entry errors to never-baited arms also resulted in a clear lesion effect ($F_{3,36} = 22.95$; $p < 0.0001$); the AT group made an average 0.39 (0.25) errors, in contrast to the absence of such errors in LT = 0.02 (0.05), MT = 0.00 (0.00) and Control = 0.01 (0.03).

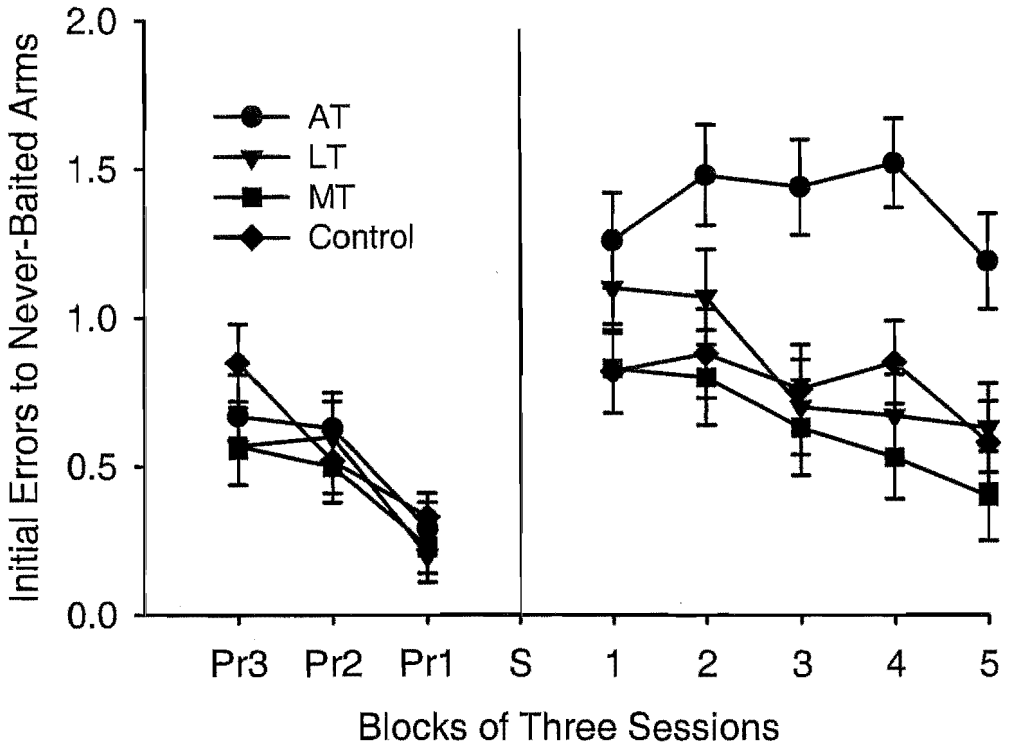

Fig. 13. Spatial Memory: mean (±SEM) number of initial errors to never-baited arms (reference memory errors) for all groups, pre- and post-operatively in the radial arm maze, separated into blocks of three sessions. Pr3, Pr2, Pr1 = last three blocks of pre-operative sessions, S = surgery.

Analysis of mean number of arm visits before an error confirmed further that only the AT group were impaired (see Fig 14A). The AT group made significantly less correct arm visits before both a working memory error, ($F_{3,36} = 15.90$, $p < 0.0001$) than the other three lesion groups, which did not differ. The mean number of correct entries before a working memory error for the AT group was 5.06, (SD = 0.73); LT = 6.75 (0.74); MT = 7.17 (0.62); Control = 7.03 (0.87)). As shown in Fig. 14B, a similar pattern of AT impairment occurred for the number of correct arm visits made before a reference memory error. Statistical analysis confirmed a lesion effect, ($F_{3,36} = 4.86$, $p <$ 0.01). The mean number of correct entries before a reference memory error for the AT group was 4.77, (0.97); LT = 6.14 (0.85); MT = 6.24 (0.97); Control = 5.75 (0.92)).

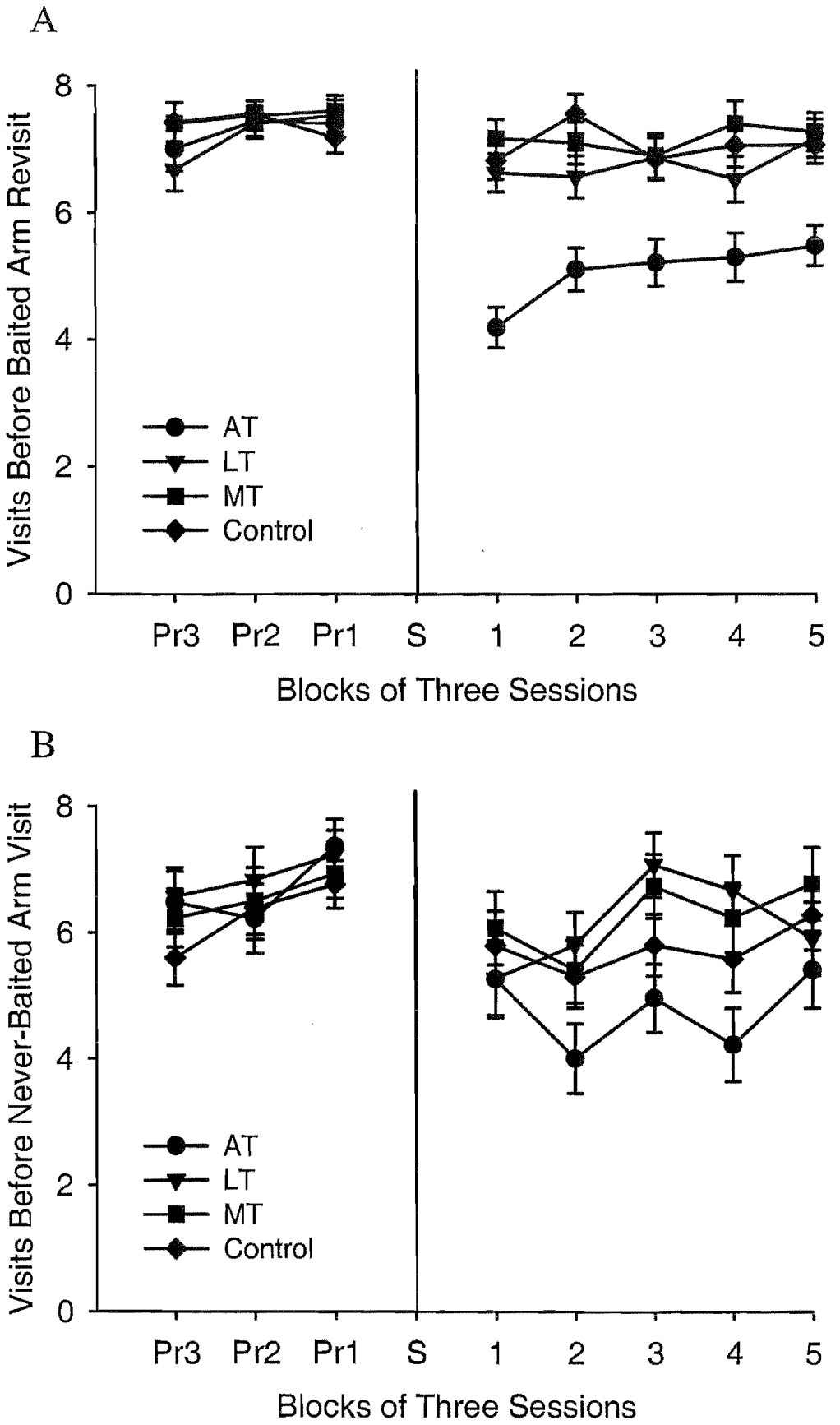

Fig. 14. Spatial Memory: mean (±SEM) number of arm visits before errors for all groups, pre- and post-operatively in the radial arm maze, separated into blocks of three sessions. (A) Visits before errors to baited arm. (B) Visits before errors to never-baited arms. Pr3, Pr2, Pr1 = last three blocks of pre-operative sessions, S = surgery

Despite the clear difference in initial performance between groups, there were no choice latency differences, either for revisits to baited arms ($F_{3,34}$= 1.70; $p > 0.2$) or for visits to never-baited arms ($F_{3,34}$= 1.44; $p > 0.3$) during the first block of 3 postoperative sessions. For the subsequent 4 blocks of testing, however, the AT group took less time to make choices than the LT, MT and Control groups, for both revisits to baited arms ($F_{3,36}$= 5.42; $p < 0.004$; the mean choice latency across blocks 2 to 5 for the AT group was 1.68s, (SD 0.47); LT = 4.86s (2.51); MT = 4.72s (2.14); Control = 4.02s (1.65)), and visits to never-baited arms ($F_{3,36}$= 3.48; $p < 0.03$; AT = 1.67s (0.71); LT = 3.46s (1.56); MT = 4.32s (2.69); Control = 3.68s (1.82)). Activity levels of rats were also measured as time in the maze divided by the number of arms visited; there was an overall group effect ($F_{3,36}$ = 12.75; p <0.001) with the activity level for the AT group being considerably shorter per arm visit, 24.05s (2.69) than all other groups, LT = 30.90s (2.51), MT = 32.12s (4.28), and Control = 30.31s (2.49).

7.8.3 Memory for the temporal order of familiar objects

Preference for two different, but familiar, objects was observed during a test trial. Rats had previously been exposed for 5-min periods to an identical pair of one of these objects 2-hours prior, and an identical pair of the second object 1-hour prior, to the test trial. The exploration time for the first identical pair of objects (A) in the study trial two hours prior to the test trial was 43.17s and the exploration time for the second identical pair of objects (B) in the study trial one hour prior to the test trial was 42.74s. Average exploration times did not differ between groups, AT = 46.54s (SD 8.22), LT = 40.87s (3.47) MT = 43.52s (8.78), and Control = 41.41s (9.14), or vary systematically between groups across study phases (group x study phase, $F_{3,36}$ = 2.34, $p < 0.09$). In the test trial, the preference for the older of the two objects was assessed as a ratio score of the exploration time of the object (A) that had been presented during the first study trial versus the exploration time of the object (B) that had been presented during the second study trial, divided by the total exploration time of both objects [(A-B)/(A+B)]. This analysis controls for individual variability in exploratory behaviour.

Although no group effect of lesion was clear across preference ratios, ($F_{3,35}$ = 2.21, p < 0.2), differences did emerge when each lesion group ratio was assessed by single sample t-test to determine whether it differed from chance preference. This post-hoc analysis is considered acceptable practise in recent journal publications that have assessed spontaneous object recognition preference ratios. The analysis compares the average

amount of exploration time for each individual lesion group with a chance level of preference, that is a discrimination ratio of zero. As Fig. 15 shows, the AT and Control groups showed a clear preference for the first of the two familiar objects presented (object A; p's < 0.002), indicating memory for the temporal order of object presentation. By contrast, the preference level shown by the LT and MT groups was not different to chance (both p's > 0.40).

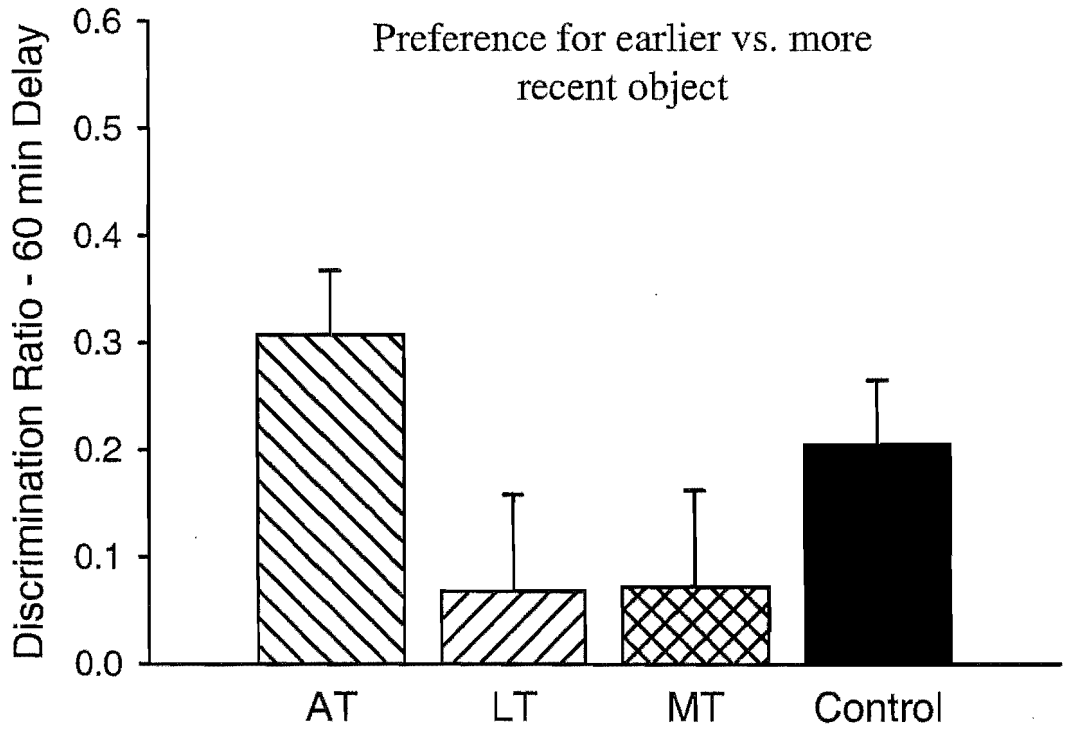

Fig. 15. Memory for temporal order of two familiar objects: Mean (±SEM) discrimination ratios for all groups during the test trial with a 60-min delay between the two study trials.

Minute-by-minute preference ratios for all four groups are shown in Fig. 16. Analysis of the differences between groups across minutes of explorations indicated no significant effect of lesion (F < 1.0), minute, (F < 1.0) or lesion x minute interaction (F < 1.0).

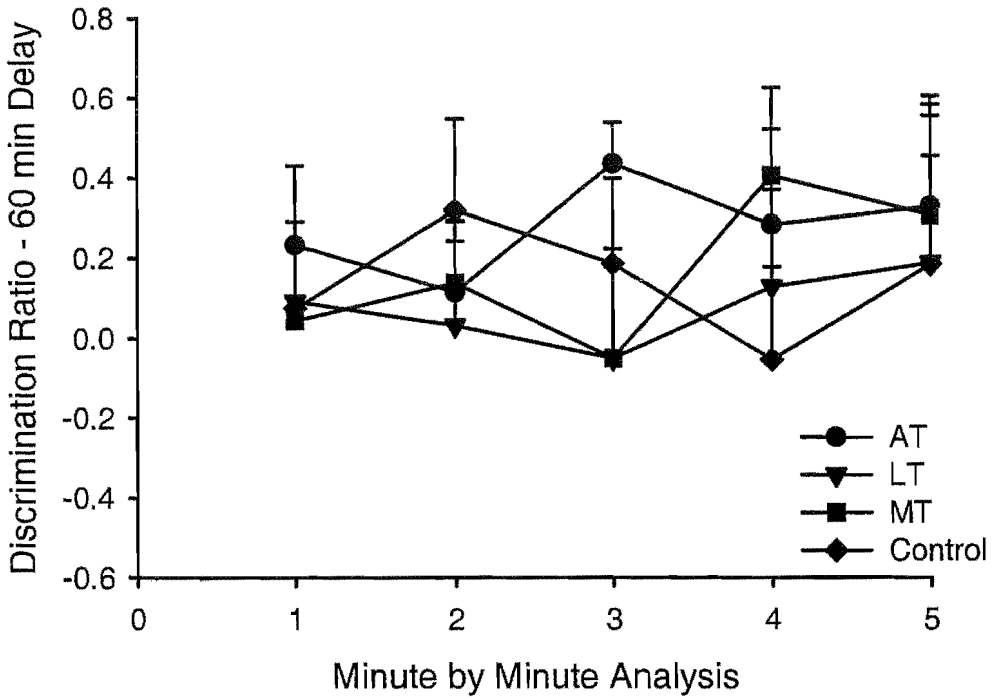

Fig. 16. Memory for temporal order of two familiar objects: Minute-by-minute mean (+SEM) discrimination ratios for all groups during the test trial.

7.8.4 Memory for familiarity versus novelty object recognition

In this task, the test trial for two different objects included one copy of an object (C) the rat had previously explored during a study trial 2 hours prior to the test trial and a second object that was completely novel (D). In the 5-min study trial, the exploration time for the two identical objects (C) tended to be higher and more variable across rats than the previous task, but there was no difference in these initial exploration times between groups, ($F_{3,36} < 1.0$); AT = 48.90s (SD = 10.88), LT = 50.72s (16.93), MT = 43.24s (14.25), and Control = 47.54s (19.84). In contrast to memory for temporal order, recognition memory, measured as total exploration time for the novel object verses total exploration time for the familiar object divided by total exploration time for both objects [(D–C)/(D+C)], was evident in all four groups, when compared to a mean of zero (p's < 0.02; Fig. 17). Although, as was the case in the temporal order memory task, the one way ANOVA revealed no clear difference between the groups, ($F_{3,36} = 1.22$, $p < 0.4$), despite the suggestion that the AT showed weaker novelty preference than the controls, this was not significant ($p < 0.1$).

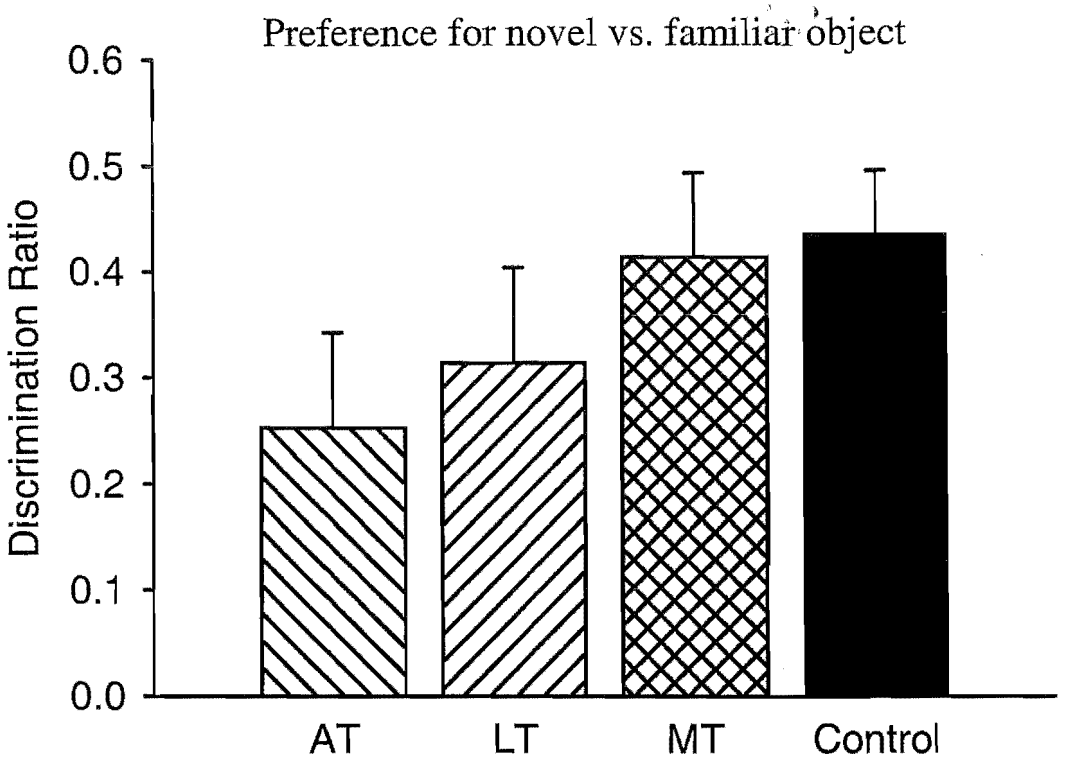

Fig. 17. Memory for familiarity versus novelty: Mean (±SEM) discrimination ratios for all groups during the test trial with a two-hour retention delay.

Additional analyses of the discrimination ratio for preference of the novel object over the familiar object during the first minute indicated no clear preference for the novel object across any of the lesion groups. First minute preference ratios for the AT, LT, MT and Control groups did not differ from chance, ($p > 0.27$, $p > 0.66$, $p > 0.83$ and $p > 0.63$, respectively).

7.8.5 Memory for reward magnitude

In this task, rats were trained to make a go/ no-go response that was contingent on the reward value of a previous reinforcer. That is, rats were trained to run quickly across a platform ("go") if they received a reward-value discriminative stimulus that signalled the availability of an additional reward and not to run ("no-go") when presented with the alternate reward-value stimulus that signalled no additional reward (contingencies for reward values were counterbalanced across rats). Within 4 to 6 blocks of 12 trials, all rats irrespective of lesion group rapidly reduced their running times to about 2s on trials when the reward-value stimulus signalled an additional reward. Increased running times also

occurred during the first half of training on trials when the no-go reward value stimulus was presented, followed by steady increases in running time latencies in all groups during the second half of training sessions (Fig. 18). A clear difference between groups emerged on the no-go trails during the latter half of training, resulting in a significant group x block interaction ($F_{33,396} = 4.68$; $p < 0.0001$). Across this latter half of training, the MT group displayed inferior performance for the no-go trials than the AT ($F_{1,36} = 23.64$; $p < 0.0001$), LT ($F_{1,36} = 14.43$; $p < 0.001$) and Control groups ($F_{1,36} = 19.43$; $p < 0.0001$), which did not differ. All groups showed equally diminished retention of performance on the no-go trials following the four-week break (block 12 compared to block 13, $F_{1,36} = 124.90$, $p < 0.0001$; group by block, $F < 1.0$). Analysis of the re-acquisition blocks 13-15 confirmed that performance improved again across these final blocks ($F_{2,72} = 55.90$, $p < 0.0001$) and that the MT group continued to perform more poorly than the other three groups ($F_{3,36} = 5.44$, $p < 0.003$; group by block, $F < 1.0$).

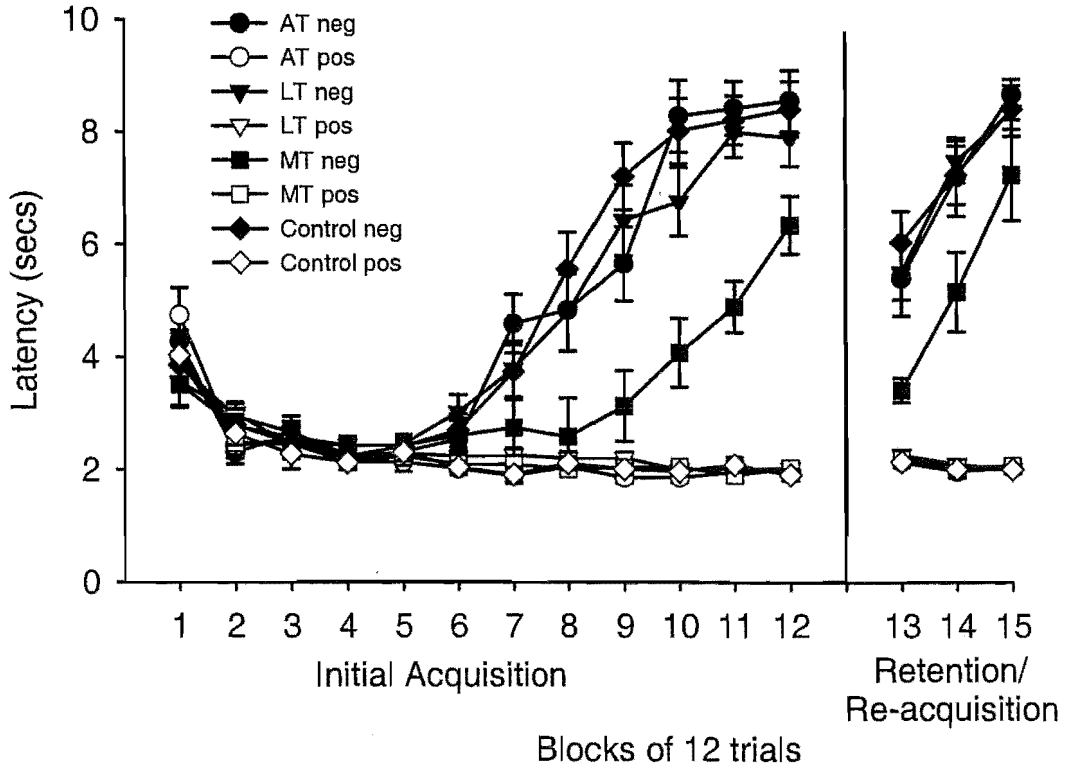

Fig. 18. Memory for reward magnitude task. Mean (±SEM) latencies for post-surgery acquisition using a conditional go (positive, pos: additional reward available) / no-go (negative, neg: no reward) procedure. All groups exhibited shorter latencies for positive trials and longer latencies for negative trials.

7.8.6 Correlations

Correlational analyses of brain damage sustained to target structures amongst all rats with medial thalamic lesions and performance on the memory tasks revealed two significant positive correlations. All medial thalamic lesion rats were included in this analysis in order to be able to gain an appreciation of the extent of damage to the medial thalamic targets of interest and the degree of impairment in the working memory tasks. First, the extent of brain damage in the AT aggregate amongst all medial thalamic lesion rats correlated with the number of errors made in the spatial task ($r = 0.89$, $p < 0.05$, Fig. 19); damage to the LT and MT aggregates was not correlated with spatial errors ($r = 0.23$ and $r = -0.18$, respectively). Even small amounts of AT damage appeared to increase errors beyond that shown by controls. Consistent with previous evidence, there was also a suggestion that substantial LT or MT damage exacerbated the effect of AT lesions on spatial memory (Warburton et al, 1999).

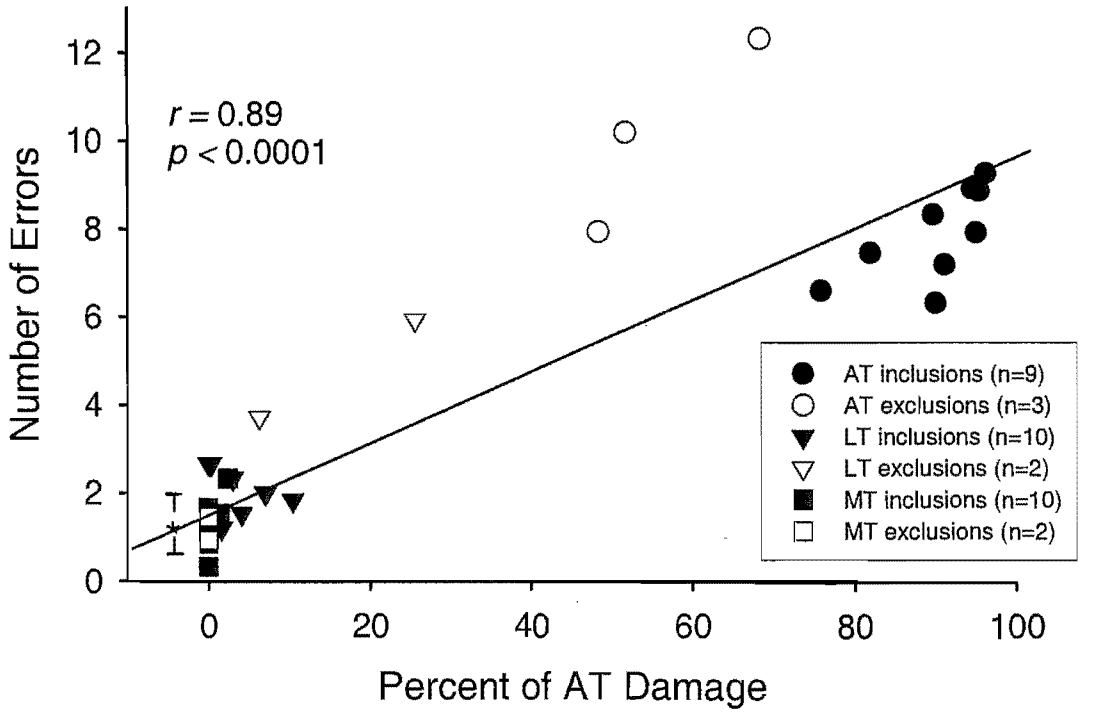

Fig. 19. A scatter plot of mean percent damage for all lesion animals (N= 36) showing the correlation between the extent of AT damage and mean errors to baited arms (working memory errors) in the radial arm task. * Control mean ± 95% confidence interval

The second significant correlational relationship was between the extent of brain damage in the MT aggregate amongst all medial thalamic rats and the number of trials required to reach the acquisition criterion in the reward magnitude task (criterion set at crossing the platform on no-go trials in > 7s per session across three consecutive sessions; r = 0.73, $p < 0.05$, Fig. 20). In general, relatively large MT damage was required to produce impaired performance on this task. Damage to the AT and LT aggregates did not correlate with trials to criterion
(r = -0.31 and r = -0.01, respectively). There were no significant correlations between brain damage sustained to the medial thalamic target regions and performance in either the temporal order memory or familiarity versus novelty detection tasks.

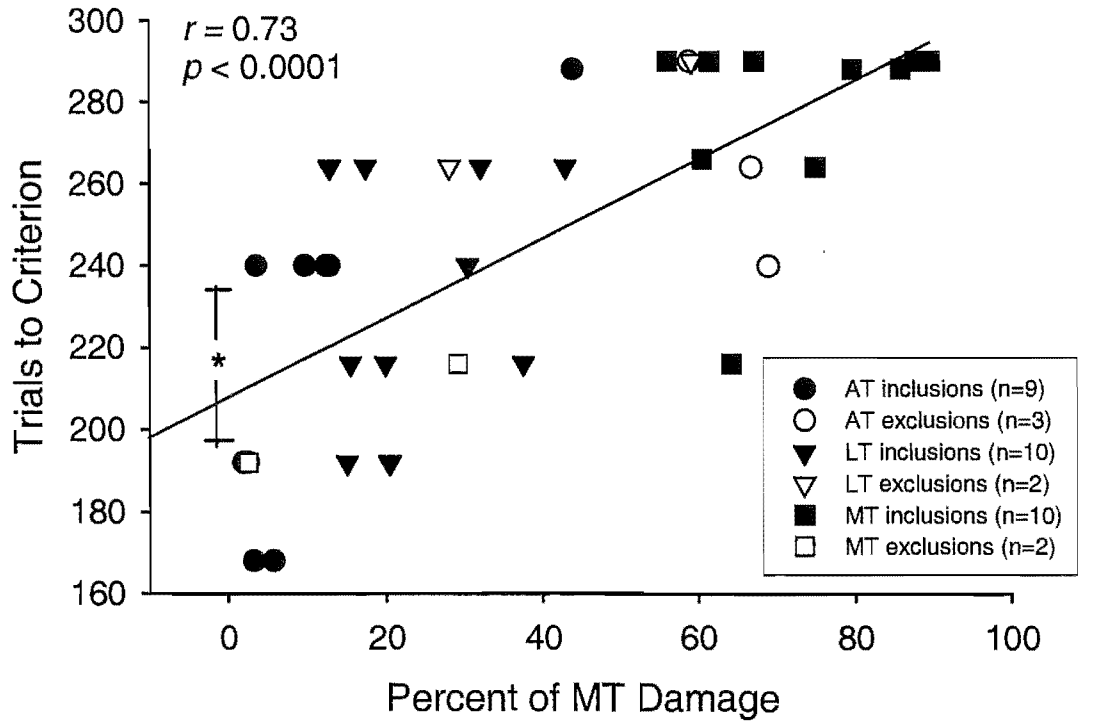

Fig. 20. A scatter plot of mean percent damage for all lesion animals (N= 36) showing the correlation between MT damage and trials to criterion (crossing the platform for neg trials in > 7s per session across three consecutive sessions) on the reward magnitude task. * Control mean ± 95% confidence interval.

7.9 Discussion

This present study provides the first direct comparison, across an array of memory tasks, of highly restricted lesions to two non-conventional aggregates of medial and non-specific thalamic nuclei and of the anterior thalamic nuclei. The three target aggregates were defined by their common significant neural connections with other cortical and subcortical structures and memory impairments after selective lesions were predicted from these interconnections with currently recognised memory processing structures (Aggleton & Brown, 1999; Kesner, 1998, 2000; White & McDonald, 2002). Only the AT lesions, but not LT or MT lesions, disrupted spatial memory, whereas only MT lesions impaired learning associated with memory for reward value. In addition, both LT and MT lesions, but not AT lesions, disrupted memory for the temporal order of familiar objects, a deficit that was not produced by any impairment in the recognition of objects per se.

The clear dissociations across memory tasks demonstrated in this first study provide new evidence that different medial thalamic regions have functional roles within multiple parallel memory systems (White & McDonald, 2002) that process specific attributes of memory (Kesner, 1998).

Spatial memory

The finding that only lesions to the AT aggregate produced severe deficits in a demanding spatial memory task, despite lengthy pre-operative training, is consistent with a previous study that showed impaired performance following AT lesions after substantial levels of pre-training using demanding procedures in water maze and T-maze spatial memory tasks (Warburton et al, 1999). The findings are also consistent with other researchers who have reported deficits in spatial memory processing using subtotal, selective lesions to anteromedial (AM) and / or anteroventral (AV) nuclei of the AT (Aggleton et al, 1996; Byatt & Dalrymple-Alford, 1996; van Groen et al, 2002).

The current findings are, however, inconsistent with studies that have reported deficits in spatial memory following lesions to either the ILn (Burk & Mair, 1998; Mair et al, 1998) or MDn (Hunt & Aggleton, 1998; Stokes and Best, 1990). The complexity of the medial thalamus and the close proximity of nuclei make it likely that that these previous ILn and MDn lesions also involved sufficient AT damage to impair spatial memory. Indeed, some deficits in spatial memory after MDn lesions have previously been attributed to those rats with additional AT damage (Hunt & Aggleton, 1998).

The above behavioural evidence suggests the importance of the AT to spatial memory. Other relevant evidence from previous neurophysiological studies has confirmed that theta rhythm activity, thought to be associated with learning and memory processing in the hippocampus, has been recorded in the AT (Vertes et al, 2001) and other functionally connected structures, for example the mammillary bodies (Kirk et al, 1996) and Gudden's tegmental nuclei of the brainstem (Kocsis et al, 2001). A related observation is that scopolamine micro-infusions into the AT produce deficits in radial maze performance (Mitchell et al, 2002), presumably by disrupting the cholinergic tegmental nuclei input, especially to the AV component (Hallanger et al, 1987). Thus, all of the above evidence confirms the particular importance of the AT within an extended hippocampal system that also includes the hippocampal region, fornix, mammillary bodies and cingulate/ retrosplenial cortices, which processes spatial memory in rats (Aggleton and Brown, 1999). Furthermore it supports the notion of a critical role for the AT in episodic memory deficits in humans (Aggleton & Brown, 1999; Harding et al, 2000; Gaffan and Parker, 2000).

There was a slight indication of improved performance shown by the rats during the final block of post-operative testing (see Fig. 12). The performance of the rats was still significantly impaired though, by comparison to all other lesion groups. Furthermore it does not seem likely that the AT lesion rats would have re-acquired the task to pre-surgery levels if the training had continued as they were more impaired at spatial memory processing throughout each block of sessions making significantly less correct visits before an error than all other lesions groups.

Memory for reward magnitude

The memory for reward magnitude task provides clear evidence of a double dissociation between the effects of AT and MT thalamic lesions. Lesions to the MT aggregate, but not the AT or LT lesions, caused deficits in the acquisition of memory for reward value (affect). Judging by the protracted acquisition required even by the control rats, this was also a demanding memory task. Previous research has demonstrated a role for the amygdala and agranular insular PFC in working memory for reward value (Kesner & Williams, 1995; Ragozzino & Kesner, 1999; DeCoteau, et al 1997). Furthermore, other researchers, using neurophysiological studies, have suggested the existence of a neural circuit consisting of the amygdala, medial MDn, and lateral PFC in rats that is involved in conditioned stimulus-reward related activity (Oyoshi et al, 1996). Therefore, the current

results implicate the MT within an amygdala memory system that includes the lateral PFC (homologous to the orbital frontal PFC in humans).

In rats, the amygdala influences stimulus-reinforcement type learning (McDonald & Hong, 2004; McDonald & White, 1993; White & McDonald, 2002). In humans, recent work suggests that the amygdala has a significant role in recognition memory for affective stimuli (Adolphs et al, 2000). Moreover, previous researchers using MDn lesions have shown related findings (see Chapter 5, for details). Briefly, MDn lesions disrupt acquisition of new stimulus-reward type associations involving objects, both in rats and monkeys (Chudasama, et al 2001; Gaffan and Murray, 1990; Gaffan et al, 1993). Thus this current evidence from the reward magnitude task suggests a similar role for the MT region.

Temporal order memory

The current findings demonstrated that the AT and control groups showed evidence of normal temporal order processing of two familiar objects, reflected by their preferential exploration of the object presented first in time. By contrast, neither the LT nor MT groups indicated a preference for either of the two objects, exploring both older and more recent familiar objects equally. The previous study on which this task was based reported impaired temporal order memory following lesions to the dorsal medial PFC in rats (Mitchell & Laiacona, 1998). Therefore the LT and MT regions, along with dorsal medial PFC, have a role in establishing memory for temporal order. Recent clinical evidence also suggests similar impairments following MDn infarcts and anatomically connected brain regions (Shuren et al, 1997; Tanji et al, 2003). It is interesting that the AT region did not produce impaired temporal order memory, given the significant neural connections between the AM nucleus of the AT region and the medial PFC (van Groen et al, 1999). The lack of an AT region effect on memory for temporal order also suggests a dissociation between this region and the hippocampal region, as the latter has been implicated in similar experimental tasks (Jobson et al, 2003; Kesner, 1998). The hippocampal region and the medial PFC are also reciprocally connected (Witter et al, 1989). Thus, the functions of the AT thalamic nuclei and their overlap with hippocampal system function may be restricted to spatial memory, but temporal order memory after AT damage warrants further extensive investigation to verify this conclusion (which is beyond the scope of this thesis).

Object recognition memory

The results of the object recognition memory task demonstrated that lesions in the medial thalamus do not disrupt the ability to discriminate between familiar and novel objects following a delay of two hours. A deficit for the MT lesion group was predicted due to the neuroanatomical connections of MDn with perirhinal and prefrontal cortical areas (Groenewegen, 1988). As detailed in Chapter 4, Aggleton and Brown (1999) proposed that the MDn and the perirhinal cortex form parts of a functional circuit involved in familiarity-based recognition memory. The current findings are consistent, however, with one study that found no deficit in object recognition memory with a 15-min delay between study and test trials following MDn lesions (Hunt & Aggleton, 1998). The involvement of the MDn in object recognition may depend on task demands. For example, MDn lesions in monkeys produce a deficit in delayed non-match to sample object recognition, which is presumed to be related to the dense connections between the magnocellular MDn (equivalent to the medial segment of mediodorsal nucleus in the rat) and the medial PFC (Gaffan & Parker, 2000).

Conclusions from this first group of behavioural tasks

Although thalamic amnesics by definition are impaired in their capacity for new learning, they display substantial variability across a variety of memory and behavioural tasks. For example, they may demonstrate deficits in recall, recognition, autobiographical memory, retrograde amnesia, and memory for temporal order (Ghida-Schmid & Bogousslavsky, 2000; Kopelman, 2000; Miller et al, 2001; Schmahmann, 2003; Shuren et al, 1997; Tanji et al, 2003). They may even show evidence of procedural memory deficits (Exner et al, 2001). They also exhibit deficits in planning, inhibition, attention and emotional responding (Benke et al, 2002; van der Werf et al, 1999, 2003). Thus it is unlikely that one specific region or fibre pathway of the medial thalamus is responsible for the degree or range of memory and other cognitive deficits observed. Instead, the current evidence from this group of behavioural tasks strongly implicates different regions of the medial thalamus in separate attributes of memory processing as a function of their significant neural connections.

Furthermore in the case of AT and MT damage, the severity of deficit is sensitive to extent of injury, which would also explain much of the variability both in human cases and in the animal lesion work (see Chapter 10 for a detailed discussion). To conclude, the current findings of double dissociations between the AT and MT aggregates have begun to provide convincing new evidence that each aggregate of medial thalamic nuclei could be a functional component of

a different memory system in the brain, which process specific attributes of declarative memory (Kesner, 1998). The task now is to further determine a functional role for the LT aggregate within a specific attribute of memory in relation to its prominent neural connections. Thus, the following group of experiments (Chapter 8) was devised to pursue this objective.

Chapter 8

Selectivity of AT and LT Thalamic Aggregates in Specific Attributes of Memory

This chapter documents the second of three experiments that was conducted to assess memory impairments following lesions to each of the different aggregates of the medial thalamic nuclei, in order to test the proposal that each aggregate is a functional component in a different neural circuit that processes a specific attribute of memory. The main behavioural task used in the current experiment assessed working memory for egocentric response. This task was contrasted with acquisition of spatial working memory in a radial maze. Rats received lesions to the AT or the LT thalamic aggregates.

8.1 Introduction

Brain damage in the medial thalamus is associated with a variety of memory and behavioural deficits. These memory deficits amongst both the human clinical cases and animal lesions of thalamic amnesia are variable in both the magnitude of impairment and the range of memory deficits. As previously mentioned, identifying the critical thalamic nucleus responsible for the memory deficits has met with several difficulties (Schmahmann, 2003; Van der Werf, et al 2003). Nevertheless experimental lesion studies have implicated the importance of the anterior (AT), intralaminar (ILn) and also the mediodorsal (MDn) thalamic nuclei to memory processing but until now they have not clearly differentiated between these regions' specific contributions to memory. Thus, clearly identifying whether the individual medial thalamic nuclei contribute to specific attributes of memory would enable further understanding about the variability of deficits in thalamic amnesia.

The assessment of prominent neural connections of the medial thalamus in this thesis (Chapter 6) indicates that the three medial thalamic aggregates targeted in the first experiment (Chapter 7) are differentially connected to other independent brain structures, which have been widely regarded as responsible for processing different aspects of memory. Moreover the first study clearly demonstrated that the different aggregates of the medial thalamic nuclei should also be considered functional components of these multiple memory systems, which are

involved in processing different attributes of memory. For example, it was evident from the findings that a double dissociation exists between the MT and AT aggregates on two different memory tasks, namely a memory for reward value task and a spatial memory task, respectively. Furthermore selective LT lesions did not produce memory deficits in either of these tasks. Thus it was concluded that these novel findings are consistent with previous research that suggests the medial MDn contributes to an amygdala-based memory system and the AT contributes to a hippocampal-based memory system (Aggleton & Brown, 1999; Gaffan et al, 1993; Oyoshi et al, 1996).

While the AT and MT were clearly dissociated in behavioural tasks, the LT group only showed disrupted memory processing for temporal order information, presumably as a function of the prominent connections between this region and the medial prefrontal cortex (PFC). Further investigation into the types of memory processing carried out by this medial thalamic region is warranted. The evidence on connections in Chapter 6 suggests that the LT may have a functional role in another independent, parallel multiple memory system, namely the dorsal striatum memory system (McDonald & White, 2002), due to its prominent connections with this region of the brain.

The memory system related to the dorsal striatum (caudate nucleus / putamen) appears to be involved in processing specific forms of memory related to response or stimulus-response associations (Kesner, 1998; White & McDonald, 2002; Packard & Knowlton, 2002). There is substantial evidence from both clinical cases and animal lesion models that demonstrate a role for the dorsal striatum in response memory. The types of tasks disrupted following damage to the caudate and dorsal striatum are procedural learning, stimulus-response associations, sequential response learning and egocentric localization, but not spatial memory (Kesner et al, 1993; McDonald & White, 1993, 1994; DeCoteau et al, 1999; Knowlton & Squire, 1995; Packard & McGaugh, 1996; Packard & Teather, 1996, 1997).

Within the dorsal striatum, dissociations have also been reported between the more dorsolateral and the more dorsomedial aspects. It is proposed that the dorsolateral striatum in particular is involved in sensorimotor function and in simple stimulus-response associations, as lesions to the dorsolateral striatum impair learned responding to local cues (McDonald & White, 1994; Devan & White, 1999). In contrast, it is proposed that the dorsomedial striatum and hippocampus are parts of a system that promotes responding based on learned cognitive-spatial information, particularly in competitive cue-place response situations, as lesions to the dorsomedial striatum impair responses based on place cues during a cue-place version of the

water maze task (Devan et al, 1999; Devan & White, 1999). Furthermore it is reported that dorsomedial striatum lesions biased the rats toward the use of stimulus-response learning in a water maze task in which competing place and cue learning preferences are simultaneously assessed (Devan et al, 1999; Devan & White, 1999). Finally McDonald and White (2002) concluded that these dissociated memory deficits between the dorsolateral and dorsomedial striatum are consistent with their respective neuroanatomical connections corresponding to the matrix and patch compartments of the dorsal striatum, respectively (White, 1989: see Chapter 6).

Different regions of the dorsal striatum are prominently connected with the prefrontal cortex (PFC) and the rostral intralaminar nuclei, and select segments of the midline and mediodorsal nuclei in the thalamus, forming a fronto-striatal-thalamic circuit (Groenewegen et al, 1990; see Chapter 6 for further details). Furthermore, there is substantial evidence that the dorsal medial PFC (dorsal anterior cingulate and precentral cortices) is also involved in response memory, that is working memory for motor responses (i.e. a left or right turn; by design a stimulus-response type task), but not spatial memory (Delatour & Gisquet-Verrier, 1996; 1999; 2001; Kesner et al, 1996; Ragozzino & Kesner, 1998). Therefore, it seems plausible that the proposed LT thalamic aggregate may also contribute a role to egocentric response type memory processes.

Previous research evaluating whether the medial thalamic nuclei are involved in egocentric response memory has thus far been limited to assessments of AT lesions. Furthermore the lack of egocentric response memory deficits following AT lesions suggests that this region does not contribute to egocentric response learning. For example, lesions of the AT did not impair the ability to learn a visuospatial conditional learning task that could be solved by associating specific body turns (e.g. an egocentric response) with visual stimuli (Sziklas & Petrides, 1999). Likewise AT lesions did not disrupt an egocentric discrimination or its reversal, that is lesions to the AT did not disrupt the ability to acquire an egocentric rule (always turn to the left or to the right) and then to reverse the reinforced turn (Aggleton et al, 1996; Warburton et al, 1997). These findings are consistent with the suggestion that the AT thalamic nuclei are a functional component of a hippocampal memory system, which if damaged, does not cause impairments in egocentric response memory tasks (Packard & McGaugh, 1996). Furthermore, triple dissociations have been reported between the hippocampus, dorsal striatum, and amygdala in tasks assessing memory for stimulus-stimulus learning, stimulus-response learning and stimulus-reward learning, respectively (McDonald &

White, 1993) and between the hippocampus, caudate nucleus, and extrastriate visual cortex in tasks assessing memory for spatial location, motor responses and objects, respectively (Kesner et al, 1993).

In order to further determine the potential contributions of the AT and LT thalamic aggregates to thalamic amnesia and establish whether a double dissociation exists in their functional contributions to different attributes of memory, the following behavioural tasks were proposed. As outlined above, the LT's connections make it likely that this region contributes to the dorsal striatum response memory system (Kesner, 1998; McDonald & White, 2002). A response task was used to test working memory for egocentric response (cf. Ragozzino & Kesner, 2001). The second task assessed acquisition of spatial working memory using an 8-arm radial maze (all arms baited) and a 5s delay between arm choices. It was predicted in the spatial memory task that only the AT thalamic lesion would produce deficits in acquisition, despite other evidence of ILn lesions in rats, which implicates a contribution of the ILn to the acquisition of spatial memory (Burk & Mair, 1998; Mair et al, 1998; Savage et al, 1997, 1998; Young et al, 1996). This prediction was based on the evidence from the previous experiment (Chapter 7), which indicated that only the AT lesions, but not the LT lesions, produced deficits in spatial memory, presumably as a consequence of disrupting the circuit of prominent neural connections between the AT and the extended hippocampal system (Aggleton & Brown, 1999). In order to be certain that the LT does not impair spatial memory, it was necessary to assess the performance of LT lesion rats during acquisition training of a spatial memory task. This was essential to determine as in the previous study (Chapter 7) spatial memory was assessed in the context of post-operative training following extensive pre-surgery training. Thus there remains the possibility that LT lesions may demonstrate a deficit if the LT lesion rats are only trained post-operatively without any prior exposure to the spatial memory paradigm.

8.2 Materials and Method

8.2.1 Subjects

As per the previous experiment, female hooded rats weighing between 180 and 220 gm at the beginning of pre-surgery training for egocentric response memory were used as the subjects in this experiment. They were housed together and were food restricted as per previous details. All testing in this experiment occurred between 0830 and 1930 hr at a rate of 5 sessions per week with one session per day. All protocols conformed to the NIH Guide for the Care and

Use of Laboratory Animals and were approved by the Animal Ethics Committee of the University of Canterbury.

8.2.2 Surgery

The general surgical procedure for this second set of rats was the same as that used in the first set of experiments, other than the modifications outlined below. In order to maintain highly localised neurotoxic lesions in the medial thalamic aggregates (for this experiment, AT and LT regions only) further reference surgeries were conducted to continue to try to improve the specificity of the lesion sites. The coordinates used and NMDA volumes infused during this second study are presented in Table 10 and further details of the changes made to the lesion coordinates and infusion volumes are detailed in the following text.

Table 10. Lesion coordinates for individual rat Bregma–Lambda (B-L) measurements and corresponding AP coordinates, as well as ML and DV coordinates, and NMDA Infusion Volumes for the Two Medial Thalamic Aggregates Assessed in the Present Study

	AT		LT		
	Ant	Post	Two Ant Sites		Post
B-L distance for coordinates					
0.60-0.61 cm	-0.245	-0.255	-0.345		-0.385
0.62-0.63 cm	-0.255	-0.265	-0.355		-0.395
0.64-0.66 cm	-0.265	-0.275	-0.365		-0.405
0.67-0.68 cm	-0.275	-0.285	-0.375		-0.415
ML	±0.123 *	±0.147 *	±0.130		±0.130
DV	-0.580	-0.555 *	-0.60	-0.56	-0.56
Volume μl	0.09 *	0.12	0.07 *	0.05 *	0.05 *

Abbreviations: Ant = anterior AP coordinates, AP = anterior-posterior direction from bregma, AT = anterior thalamic lesion, DV = dorsal-ventral direction from dura, LT = lateral medial thalamic lesion, ML = medial-lateral direction from midline, Post = posterior AP coordinates; * indicates the changed coordinates and volumes to those that were used in the first study.

Only slight changes were made to the lesion coordinates for AT lesions, with the ML coordinates at the anterior AP site moved to ± 0.123 cm, while at the posterior AP site, the ML was changed to ± 0.147 cm and DV changed to – 0.555 cm. The infusion volume for the AT anterior AP site was reduced to 0.09 μl but the AT posterior AP site volume remained at 0.12 μl. For the LT lesions, all coordinates remained the same but the volumes for all infusions were reduced; at the dorsal anterior AP site the volume was reduced to 0.07 μl and at the ventral anterior AP site it was reduced to 0.05 μl, and at the posterior AP site the volume was reduced to 0.05 μl.

Sham lesion controls also received surgery but with no infusion using the same coordinates with modifications as per above and procedure from the first experiment.

8.2.3 Histology

The histological procedure was the same as that previously used in the first study and the same criteria for inclusions and exclusions of rats in the behavioural analyses as per brain damage in the medial thalamus was maintained.

8.3 Working Memory for Egocentric Response

8.3.1 Apparatus

The apparatus for this task consisted of a clear perspex 'plus' maze, positioned upon a solid table, elevated 700 cm above the ground. The plus maze had four arms that were 55 cm long and had 22 cm high walls. Clear perspex blocks that slid along the insides of the arms guided the rats to make either a right or left 90-degree angle turn or created a T-maze design during the choice phase of each trial. All testing was conducted with only a red darkroom light directly beneath the table for the experimenter (i.e. effectively in the dark for the rats). A curtain surrounded the maze and an infrared camera relayed behaviour in the plus-maze as per the previous experiment.

8.3.2 Procedure

Rats received pre-surgery training in the egocentric response task and were always carried into the room in an opaque covered cage with the lights out. The rats were familiarised to the plus maze with 0.1 gm chocolate chip pieces scattered throughout the arms, initially as cage mates and then individually for five days prior to commencing training in the egocentric

response task. Training used a delayed matching-to-sample procedure with 12 trials per session, five sessions per week.

Within a session, six of the trials incorporated a forced left turn and 6 trials had a forced right turn (study phase), randomised using Fellows (1967) sequences. During the study phase a perspex block was positioned in the maze, which forced the rat to make either the left or right 90-degree turn and the rat was then rewarded with a chocolate chip (0.1 gm) at the end of the arm. Following a delay of 10s, the test phase began. During the test phase, the arm entered in the study phase was used as the start arm and the clear Perspex block was re-positioned to form a T-maze so that the rat could make a choice of either a 90-degree left or right turn. Rats were rewarded (1 x 0.1 gm chocolate piece) for matching-to-sample, that is, choosing to make the same body turn that they had been forced to make during the study phase of each particular trial. The floor and walls of the maze arms were wiped using a weak detergent solution during each delay and between each trial and the experimenter changed positions in the room throughout the trials for each rat. The inter-trial interval was 15s.

Rats were trained until they reached above 75% correct delayed matching-to-sample (DMS) choices across 10 consecutive pre-operative sessions (Ragozzino & Kesner, 1999). It took approximately 90 pre-surgery sessions to reach and maintain this criterion. All rats were matched for performance and randomly assigned to one of three groups to receive surgery for lesions to either the AT or LT regions of the medial thalamus or sham-lesion controls. Following 10 days of post-operative recovery, during which time the 85% weight reduction was re-established, the rats received 2 blocks of 10 sessions each using a 10s delay and 1 block of 10 sessions using a 20s delay between forced and free choices as per the pre-surgery training procedure.

Once the rats had completed the working memory for egocentric response task using the two different delays (10s and 20s) between the study and test phases of the trial, their post-operative acquisition of a spatial memory task was assessed using an 8-arm radial maze. The spatial memory assessment occurred approximately 8 weeks after surgery.

8.4 Acquisition of Spatial Working Memory

8.4.1 Apparatus

The radial maze was of identical design to the one used in the first study (Chapter 7) but with only 8 arms and a smaller 35 cm central hub. Clear Perspex guillotine doors that could be raised singly or as one unit governed access to each arm.

8.4.2 Procedure

Rats were familiarised post-operatively to the radial maze with chocolate chip pieces scattered throughout the arms, initially as cage mates and then individually across five days. The chocolate was gradually moved towards the ends of all arms and was only present in the food wells on the final familiarisation day. Rats then received one training session per day, five-days a week. At the beginning of each session, all of the arms were baited and the rat was placed in the central hub with all the doors closed. All of the doors were then raised simultaneously allowing the rat a choice of any arm to enter. Once the rat entered an arm, all other doors were lowered and on returning to the central hub, the remaining door was lowered. After a 5s delay, all eight doors were raised again allowing for another choice to be made. A session was complete once the rat had entered all eight baited arms or 10 min had elapsed. Acquisition training in the 8-arm radial maze task continued for 15 sessions.

8.5 Data Analysis

In the working memory for egocentric response task, differences between the lesion groups were assessed using repeated-measures ANOVA for the number of correct DMS choices made, averaged across blocks of 10 sessions. Analyses included a comparison of the final block of 10 pre-operative sessions (Pre) and the 1st block of post-operative 10s delay sessions (PST1), a comparison between PST1 and the 2nd block of post-operative 10s delay sessions (PST2) and a comparison between PST2 and the 20s delay sessions (PST3). In acquisition training of the radial maze spatial memory task, differences between the lesion groups were assessed using repeated measures ANOVA for the number of revisits (errors) made, the number of arm visits made before an error and differences across choice latency to correct and incorrect arm visits, averaged across blocks of three sessions.

8.6 Results

8.6.1 Histology

The minimum and maximum extent of acceptable lesions for all groups are shown in Fig. 21A and B (p. 163). As was the case in the first set of experiments, acceptable lesions met the arbitrary criterion of at least 50% damage to the intended aggregate and less than 50% damage to either of the alternate aggregates (the MT aggregate was included to be able to infer whether the lesions also effectively excluded this target region).

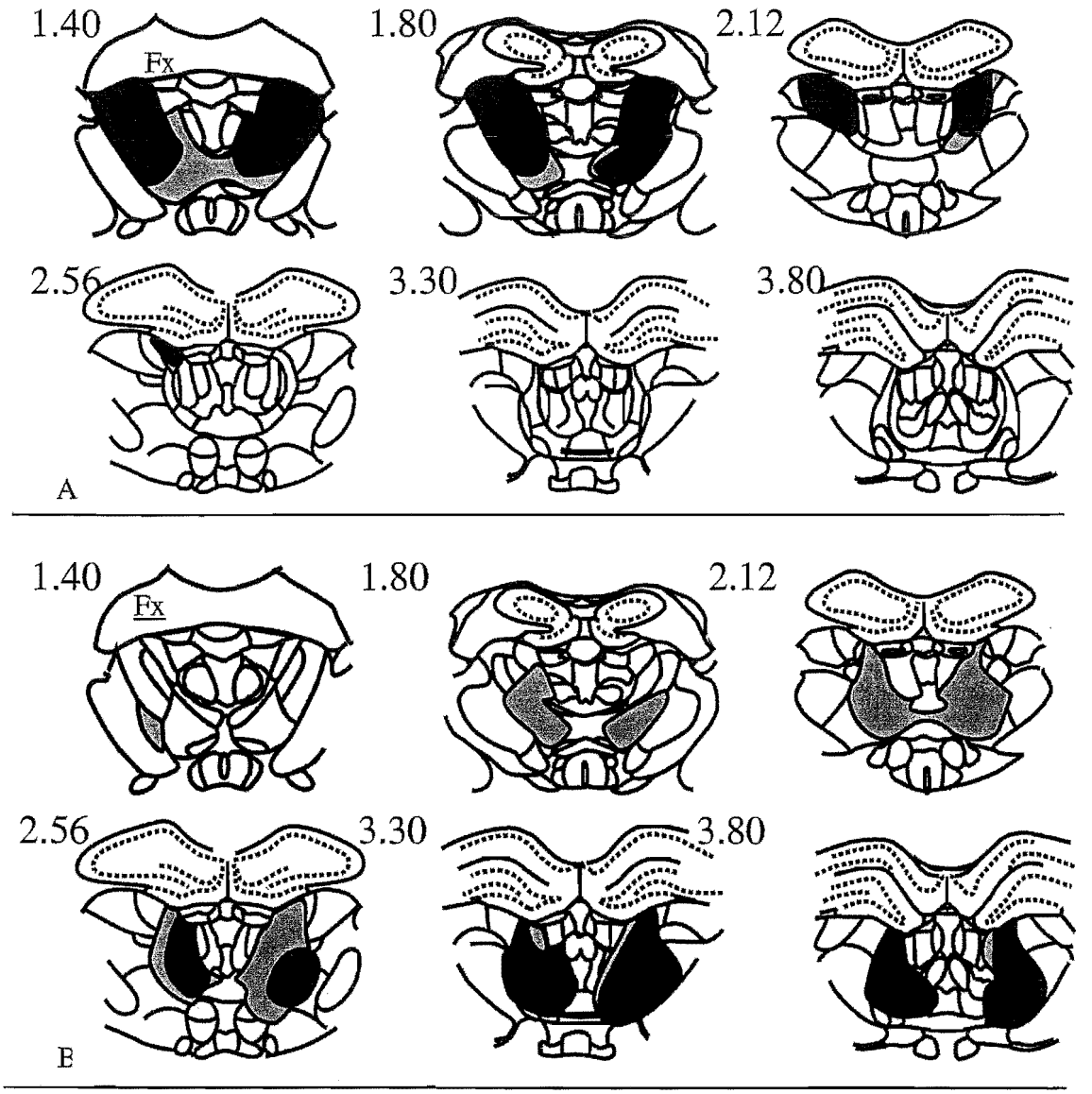

Fig. 21. A series of coronal sections throughout the medial thalamus showing the area of cell loss with the smallest (*black*) and largest (*gray*) thalamic lesions. A: Anterior thalamic rats (AT). B: Lateral thalamic rats (LT). Coronal sections are adapted from Paxinos and Watson (1998) and coordinates are mm from bregma.

In all acceptable lesions, damage was relatively large in the target regions and unintended damage to other thalamic structures was relatively minor (see Table 11, p. 165). The slight adjustments in surgery coordinates and infusion volumes from those used in the first study (Chapter 7) increased the specificity of lesions for both the AT and LT aggregates and further reduced any additional damage to adjacent thalamic structures. Two AT lesion rats were excluded because neither received sufficient damage to the intended aggregate (in the spatial memory task ranked 10th and 24th worst out of 26 rats in total; both were similar to the Control rats in the egocentric response task). Two LT lesion rats were excluded. One of these sustained sufficient LT damage but also substantial damage to the MT region and some (19%) damage to the AT aggregate (poor on the egocentric response task, ranked 6th worst, and also poor on the spatial task, ranked 7th worst). The other LT exclusion had too little damage to the LT region, some damage in the MT region and no damage in the AT (ranked 16th worst in the egocentric response task and 26th worst in the radial maze task).

Table 11. Median (Range) of Bilateral Damage to the AT and LT Medial Thalamic Aggregates and Adjacent Medial Thalamic Nuclei (including the MT Medial Thalamic Aggregate) following micro-infusion of NMDA.

Region	AD	AM	AV	Total AT %	CL	MDl / MDpl	PC	rCeM	Total LT %	IMD	MDc	MDm	Total MT %	IAM	LD	PT	PVA	PV/ PVP	Re/ Rh
Group																			
AT n= 6	90.9 (78.2-99.8)	69.1 (40.5-92.5)	91.5 (71.5-100)	84.7 (78.8-93.6)	10.6 (7.0-31.5)	0.6 (0.0-9.7)	15.3 (12.7-32.1)	2.2 (0.4-17.9)	8.4 (7.0-23.1)	0.0 (0.0-0.0)	0.0 (0.0-0.3)	0.0 (0.0-0.0)	2.2 (0.9-3.3)	24.2 (4.8-62.5)	10.0 (0.6-18.2)	17.5 (2.6-39.8)	0.0 (0.0-0.2)	0.0 (0.0-0.0)	0.0 (0.0-1.1)
LT n= 7	6.8 (0.0-6.5)	3.9 (0.0-39.2)	1.0 (0.0-33.1)	2.4 (0.1-21.5)	80.1 (63.2-87.1)	74.7 (49.0-100)	61.8 (58.1-68.7)	16.0 (0.9-64.4)	66.5 (54.7-76.6)	2.2 (0.0-18.8)	49.5 (39.5-64.7)	22.5 (14.5-45.2)	26.3 (22.5-43.0)	0.1 (0.0-33.6)	1.8 (0.0-21.2)	0.0 (0.0-4.3)	0.0 (0.0-0.0)	0.0 (0.0-3.5)	0.0 (0.0-14.4)

Abbreviations:

AD= anterodorsal nucleus; AM= anteromedial nucleus; AV= anteroventral nucleus; CL= centrolateral nucleus; IAM= interanteromedial nucleus; IMD= intermediodorsal nucleus; LD= laterodorsal nucleus; MDc= central segment of mediodorsal nucleus; MDl= lateral segment of mediodorsal nucleus; MDm= medial segment of mediodorsal nucleus; MDpl= paralamellar segment of mediodorsal nucleus; PC= paracentral nucleus; PT= parataenial nucleus; PV/ PVP= paraventricular nucleus/ posterior paraventricular nucleus; PVA= anterior paraventricular nucleus; rCeM= rostral region of central medial nucleus; Re/ Rh= reunions nucleus/ rhomboid nucleus; Total AT%= total percent damage to anterior medial thalamic target; Total LT%= total percent damage to lateral medial thalamic target; Total MT%= total percent damage to posteromedial thalamic target.

8.6.2 Memory for Egocentric Response

Rats were preoperatively trained in the egocentric response task and then retested postoperatively. As Fig. 22 shows, prior to surgery, there was no difference in performance between the three groups ($F < 1.0$). Post-operatively, the LT group showed marked impairments in working memory for egocentric responses that persisted across post-operative blocks of 10s delay trials (PST1 and PST2). In contrast, AT lesion rats were comparable to controls. Analysis of the immediate effects of lesions on post-operative performance (Pre compared with PST1) demonstrated a clear effect of block, ($F_{1, 19} = 29.58, p < 0.0001$) and a significant lesion x block interaction, ($F_{2, 19} = 5.91, p < 0.01$). Simple main effects analysis confirmed that only the LT lesion group was significantly impaired ($p < 0.0001$) at making correct DMS choices during the PST1 block compared with the Pre levels. Furthermore simple main effects analysis confirmed that the LT group was significantly different to the Control ($p < 0.007$) and AT ($p < 0.03$) groups during the PST1 block. The small reduction in correct DMS choices for the AT and Control groups was not significant.

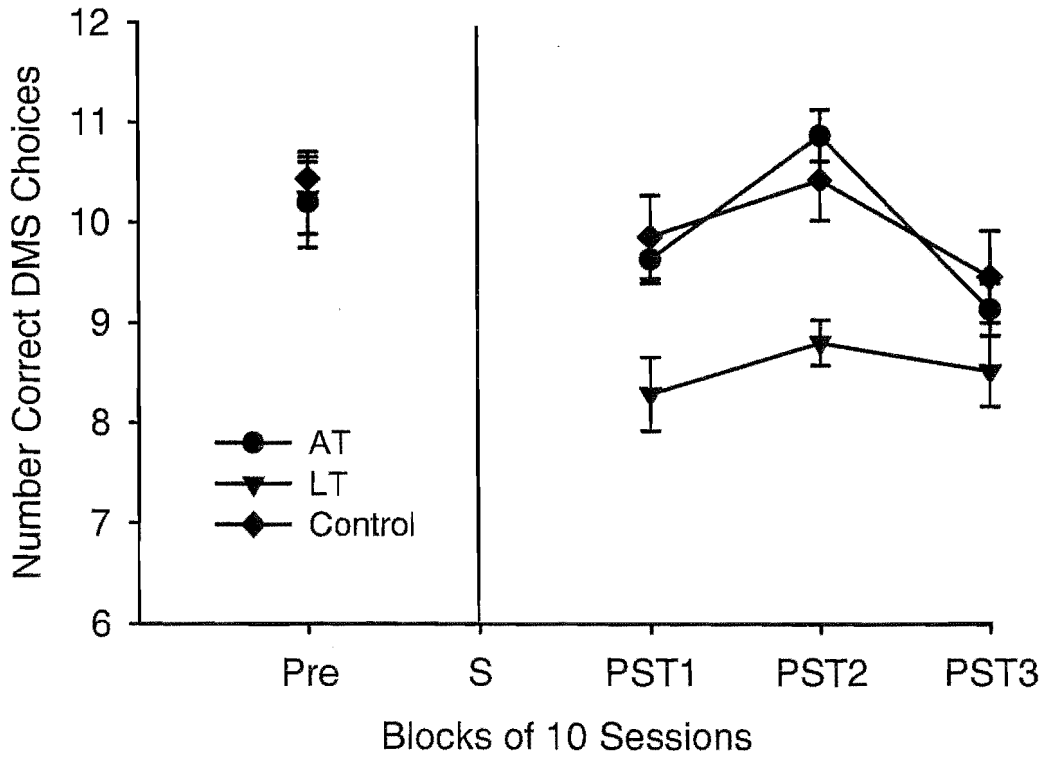

Fig. 22. Egocentric Response Memory: Mean (±SEM) number of correct delayed match-to-sample (DMS) choices made for all groups, in blocks of 10 sessions. Pre = last 10 pre-surgery training sessions using a 10s delay between study and choice phases of the trial, S = surgery, PST1 = first block and PST2 = second block of post-operative sessions using a 10s delay between study and choice phases, PST3 = third block of post-operative sessions using a 20s delay between study and choice phases.

Analysis of the PST2 block compared to the PST1 block demonstrated a significant effect of lesion, ($F_{2, 19} = 8.29, p < 0.003$), with the LT group making less correct choices across both PST1 and PST2 blocks than either the AT ($p < 0.005$) or Control ($p < 0.003$) groups, which did not differ. A block effect was also apparent ($F_{1, 19} = 19.76, p < 0.0003$), but there was no lesion x block interaction ($F_{2, 19} = 1.62, p > 0.2$), which indicated that all groups had improved across post-operative sessions, with the AT and Control groups showing mean performance equivalent to their pre-operative levels on PST2.

Analysis of the effects of extending the delay to 20s between the study and test phases (PST3 compared with PST2) revealed a significant lesion x block interaction, ($F_{2, 19} = 6.96, p < 0.005$). Simple main effects analysis confirmed that only the AT and Control groups were significantly impaired by the increase in delay, making fewer correct DMS choices ($p < 0.0001$ and $p < 0.001$, respectively), whereas there was no significant change in the LT group, which did not perform more poorly with the increase in delay ($p > 0.3$). The analysis also confirmed a significant effect of lesion, ($F_{2, 19} = 4.62, p < 0.02$), although this difference was only evident across blocks of sessions rather than within the PST3 block. There was also a significant block effect, ($F_{1, 19} = 43.5, p < 0.0001$) which confirmed that the increase in the delay to 20s significantly decreased the number of correct DMS choices made.

8.6.3 Spatial Working Memory

Following completion of the egocentric response tasks all rats were familiarised and received post-operative acquisition training in a standard all-arms baited version of an 8-arm radial maze task. As shown in Fig. 23, the number of errors for the first block of trials for all groups was relatively high reflecting the initial stages of acquiring a new task. However, from the second block of trials onwards clear differences emerged between the lesion groups; the errors for the AT group increased and continuing to stay high across blocks of sessions, whereas the errors for both the LT and Control groups decreased comparatively to very few errors across blocks of sessions. Statistical analysis of the number of errors made in the radial maze confirmed a significant effect of lesion, ($F_{2, 19} = 71.04, p < 0.0001$) and block, ($F_{4, 76} = 8.74, p < 0.0001$). There was also a significant lesion x block interaction, ($F_{8, 76} = 6.21, p < 0.0001$). Further post hoc analyses revealed that only the AT group continued to make many errors to the previously baited arms, averaging 7.52 errors (SD = 0.88) across blocks of sessions whereas both the LT and Control groups reduced their errors from block two onwards to very few, i.e. errors for the LT and Control groups at the end of training < 1.0. In addition the LT and Control groups acquired the task at equal rates of performance.

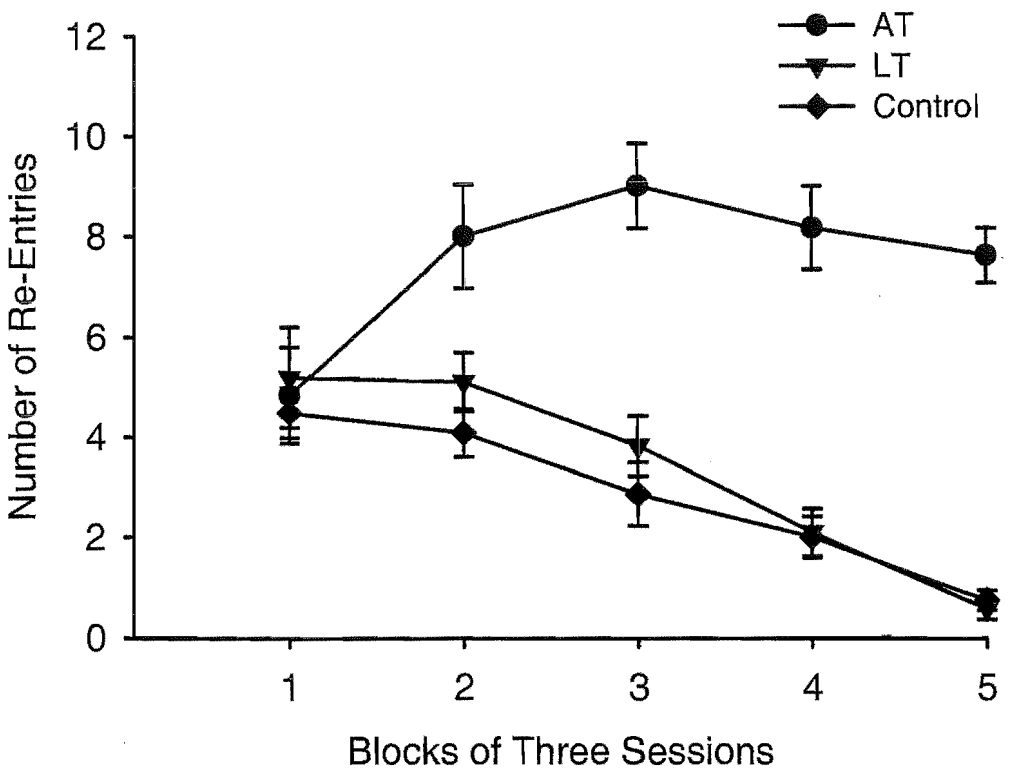

Fig. 23. Spatial Memory: Mean (±SEM) number of re-entries to baited arms (errors) for all groups, during post-operative acquisition training of an all arms baited version of an 8-arm radial maze task.

Analysis of the number of correct visits made before an error (revisit; see Fig. 24) indicated that only the AT group made significantly fewer correct visits before an incorrect visit ($F_{2,19} = 47.97$, $p < 0.0001$), compared to either LT or Control groups, which did not differ. There was also a significant block effect, ($F_{4,76} = 24.31$, $p < 0.0001$) and significant lesion x block interaction, ($F_{8,76} = 2.49$, $p < 0.02$). Post hoc analyses revealed that the AT group made their first error significantly sooner during blocks of post-operative training sessions than either the LT or Control groups, who both improved at equal rates across blocks of training sessions.

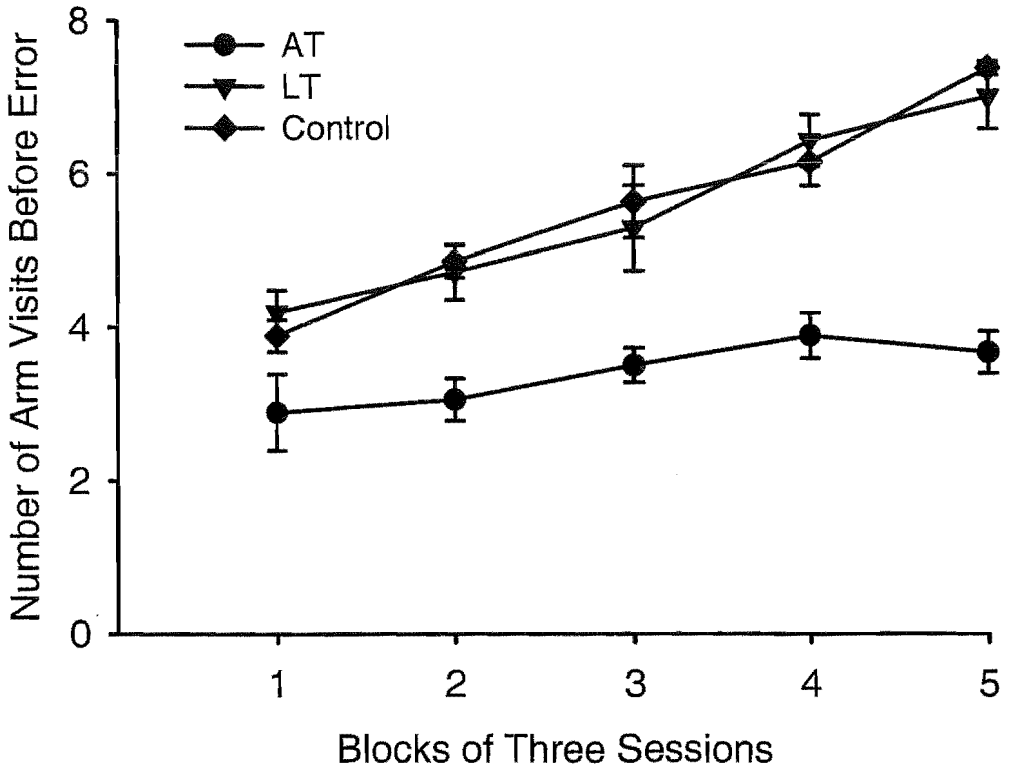

Fig. 24. Spatial Memory: Mean (±SEM) number of correct arms visits made before an error (revisit) for all groups during post-operative acquisition training of an all arms baited version of an 8-arm radial maze task.

Analysis of choice latencies revealed no clear differences between the groups for either correct arm visits ($F < 1.0$; see Fig. 25A) or incorrect arm visits ($F < 1.0$; see Fig. 25B) during blocks of training. There were clear choice latency differences across blocks of sessions for both correct arm visits ($F_{4,76} = 7.80$, $p < 0.0001$) and incorrect arm visits ($F_{4,76} = 5.95$, $p < 0.001$), which revealed that all rats increased their speed to respond as training progressed across the blocks of post-operative training sessions.

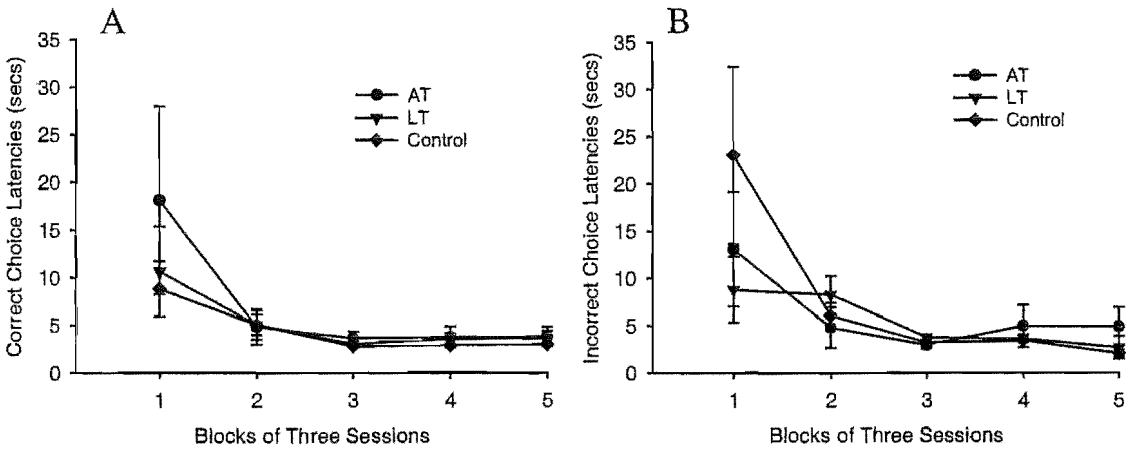

Fig. 25. Choice Latencies for the Spatial Memory Task: Mean (±SEM) latencies for all groups during post-operative acquisition training of an all arms baited version of an 8-arm radial maze. (A) Choice latencies when making a correct arm visit. (B) Choice latencies when making an incorrect arm visit.

8.6.4 Correlations

There were significant correlations between the extent of damage in the LT and AT aggregates and performance on both the egocentric response memory and spatial memory tasks. However, these correlations were over-inflated, due to the polarities in the extent of lesion damage and performance in the tasks. Further analyses between the extent of damage in the LT lesions rats that were included in the between-groups analyses and the number of correct DMS choices made during the blocks of 10s delay sessions in the egocentric response memory task just failed to reach significance, $r = -0.75$, $p < 0.051$ (see Fig. 26). The larger amounts of LT damage appeared to reduce the number of correct DMS choices made during the 10s delay on the egocentric response memory task. There was no significant correlational relationship between the extent of brain damage in the AT lesion rats included in the between-groups analyses and performance on the spatial working memory task, $r = -0.02$.

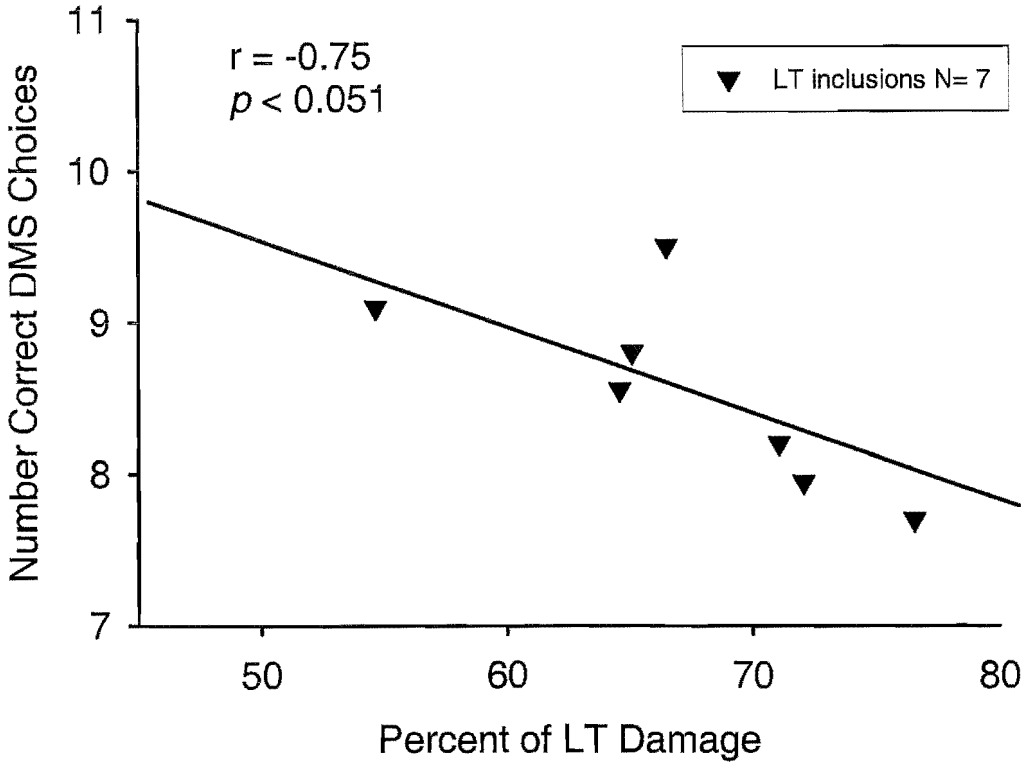

Fig. 26. Scatter plot of mean percent damage for all LT lesion inclusion rats (N= 7) and performance during the blocks of 10s delay sessions for the egocentric response memory task.

8.7 Discussion

This second study investigated whether any dissociable involvement of the LT and AT aggregates exists in processing information related to different attributes of memory, namely memory for egocentric response and memory for spatial cues. As was the case in the first study, the independent target aggregates had been defined by their respective prominent neural connections with other cortical and subcortical structures. The expected memory impairments were predicted based on the proposal that each of these medial thalamic aggregates contributes to an independent memory circuit associated with specific attributes of memory (Aggleton & Brown, 1999; Kesner, 1998; White & McDonald, 2002). The present study provided evidence of a double dissociation. Only the LT lesions, but not AT lesions, disrupted working memory for egocentric responses, whereas only the AT lesions impaired acquisition of spatial working memory. Thus the LT and AT aggregates of the medial thalamus are selectively involved in different attributes of event-based memory, namely response and spatial memory, respectively (Kesner, 1998).

Response memory

The results clearly demonstrated that lesions to the LT aggregate, but not the AT lesion, caused deficits in working memory for egocentric response. Previous research has demonstrated a role for the dorsal striatum, but not the hippocampus in memory for motor response, egocentric localisation and stimulus-response association learning (Cook & Kesner, 1988; Kesner et al, 1993; McDonald & White, 1993; Packard & McGaugh, 1996). Additional evidence suggests a role for the dorsal medial PFC in working memory for egocentric response and response selection (Delatour & Gisquet-Verrier, 1997; 1999; Ragozzino & Kesner, 2001). Therefore the current results indicate a functional role of the LT within a dorsal striatum memory circuit (McDonald & White, 2002) that also includes the dorsal medial PFC in the processing of egocentric (stimulus-response) information.

Further evidence from a neurophysiological study of lateral MDn neurons in rats has suggested the existence of a neural circuit, consisting of the anterior cingulate cortex (dorsal medial PFC), dorsal striatum and lateral MDn, which is proposed to be involved in conditioned behaviour-related (motor) activity (Oyoshi et al, 1996).
Interestingly, the LT lesions appeared to cause delay-independent deficits, which is similar to previous reports that demonstrate delay-independent deficits in memory processes following lesions to the ILn (e.g. Mair et al, 1998; Young et al, 1996; see Table 3, Chapter 5). As yet it remains unclear what specific role the LT may contribute to the dorsal striatum memory system. In relation to ILn involvement in memory processes, Mair et al (2003) suggest that cognitive and behavioural disruptions after ILn lesions are due to their active role in the ascending reticular formation that has been implicated in the activation of functions in the cortex and the striatum. Furthermore, clinical evidence suggests that the rostral ILn are specifically related to 'cognitive awareness', due to their prominent prefrontal cortical connections, that is the ability to make flexible use of cognitive strategies, the central aspect of the dysexecutive syndrome (Van der Werf et al, 2002).

Nevertheless the selectivity of memory disruptions produced by LT damage demonstrated both in this current study and in the first study (Chapter 7) implies a functional contribution of the LT aggregate to certain attributes of memory. As opposed to just a more generalised pattern of memory impairments caused by disruptions to arousal, attentional or motivational processes in association to its PFC connections. Thus the current evidence provides an initial framework for future investigation of the specific functional roles the LT may contribute to memory.

Spatial memory

There was a double dissociation between effects on memory processing tasks and LT and AT thalamic lesions. The finding that only lesions to the AT aggregate produced severe deficits in spatial memory is consistent with the results from the first study. As discussed in Chapter Seven, the finding that only the AT lesion produced deficits in spatial memory is consistent with several previous studies that also had selective lesions to the AT, or AM and AV sub-nuclei (Aggleton et al, 1996; Byatt & Dalrymple-Alford, 1996; Moran & Dalrymple-Alford, 2003; van Groen, Kadish & Wyss, 2002). This evidence further confirms the contribution of the AT within an extended hippocampal system, which is particularly important for spatial memory processing in rats, analogous to episodic-like memory in humans (Aggleton & Brown, 1999; Aggleton & Pearce, 2001; Gaffan & Parker, 2000).

The current findings did not support a role for the LT thalamic aggregate in acquisition of spatial working memory. This finding is not consistent with previous studies that have reported ILn deficits in spatial memory (Burk & Mair, 1998; Mair et al, 1998; Savage et al, 1997, 1998; Young et al, 1996). In some respects it is difficult to pinpoint why these conflicting results occur. As mentioned during the discussion of results from the first study, the nuclei of the medial thalamus are small and the regions of interest are located adjacent to one another, therefore it seems likely that the lesions to the ILn encroached into the adjacent AT and MDn thalamic nuclei. Savage et al (1997) indicate that additional damage was sustained in the midline and AT thalamic nuclei as well as the mammillary bodies, following carefully placed radio-frequency lesions within the L-IML / PC and CL intralaminar nuclei. Furthermore, in the schematic diagrams of lesions depicted by other researchers it appears that significant neurotoxic (NMDA) lesion damage has been sustained to the medial thalamic nuclei, including the AT and MDn of particular interest to this thesis (Burk & Mair, 1998). Thus further investigation is warranted. On the other hand, the extent of damage sustained to the medial thalamus in general may cause additive deficits in performance because, if the current research hypotheses are true, each medial thalamic aggregate of interest is a functional component of independent multiple memory circuit operating in parallel to process the same information. Hence lesions of the ILn that had extended into adjacent nuclei could be disrupting the processing of several independent memory systems because the behaviour observed in any task may be an aggregation from several different memory processes and strategies (see further discussion in Chapter 10).

In the current spatial working memory task, as was also observed in the spatial memory task from the first study, there was some evidence of an increase in spatial ability

characterized by a slight decrease in the number of errors made by the AT lesion rats during the final block of training sessions (see Fig. 23). As was discussed in the first experiment, it does not seem likely that the AT lesion rats will ever perform as well as the Control or LT lesion rats in the task because of their inability to commit to memory their previous visits in the maze, indicated by the consistently low mean number of correct arm visits made before an error. Additional support comes from another study in which AT lesions continued to cause severe disruptions in post-operative acquisition training of an all arms baited 8-arm radial maze task over 20 sessions (Sziklas & Petrides, 1999).

As indicated from the first study, correlational relationships between memory impaired performance and the extent of damage to the AT and MT aggregates were evident. The current study also provides evidence of a correlational relationship between severities in memory deficits during the 10s delay sessions in the egocentric response task and the extent of brain injury to the LT aggregate. This further confirms the notion that complete lesions are not essential for deficits. Furthermore one LT lesion rat excluded from the between groups analyses due to the extensive additional damage in the MT aggregate and some additional damage to the AT aggregate demonstrated relatively severe memory deficits on both of the memory processing tasks. This rat performed relatively worse than the majority of other rats with selective lesions to the individual aggregates (see Chapter 10 for further discussion). Thus this evidence is suggestive of the additive nature of the memory deficits, which may further implicate different medial thalamic regions in different attributes of memory.

The following experiment (Chapter 9) investigated the effects of lesions to the LT and MT aggregates on a test that is reported to be sensitive to PFC lesions. This following study was conducted in order to assess whether lesions to these two aggregates caused the memory deficits associated with the current and previous study. Or was it rather that these memory deficits displayed following LT and MT lesions were the outcome of a primary disruption to attention or response inhibition.

Chapter 9

Medial Thalamic Involvement in Executive Functioning: Assessment of Prefrontal Cortex-Sensitive Tasks

This chapter details the final study of the current research. This study was conducted to assess whether lesions to the different aggregates of the medial thalamic nuclei, namely the LT and MT, cause disruptions in prefrontal cortex-sensitive tasks. Behavioural assessments in this study involved two tasks that are sensitive to disruption of lesions in the medial prefrontal cortex (PFC), namely a sustained attention / response inhibition task and memory for temporal order. The memory for temporal order task was adapted from the first study (Chapter 7) and involved further re-assessments of the effects of lesions to the LT and MT aggregates using different delays between presentations of the objects during the two study trials. In the third task of this study, recognition memory for familiar versus novel objects was also re-assessed to determine whether the rats could remember familiar objects at the longest delay.

9.1 Introduction

Variability in other cognitive and behavioural deficits also occurs amongst individual cases of diencephalic amnesia, including impairments in aspects of attention, motivation, inhibition, and planning; these deficits may confound the analyses of associated memory deficits, especially in relation to the conclusions drawn from the previous two studies. Recent evidence from both a meta-analysis of thalamic infarcts reported in the literature (Van der Werf et al, 2000) and a separate assessment of thalamic infarct patients (Van der Werf et al, 2003) has concluded that disruption to the AT (mainly via injury to the mammillothalamic tract (MMT)) is solely responsible for the memory disorders of thalamic amnesia, in relation to declarative memory. In contrast, it was concluded that injury to the MDn, ILn, and midline thalamic nuclei is associated with deficits in executive function and more complex attentional impairments, in accord with prefrontal cortex associated syndromes rather than amnesia, per se. Anatomical studies have proposed that the ILn play a role in attention by modulating arousal of cortical areas due to the prominent inputs to the ILn from the ascending reticular formation of the brainstem (Berendse & Groenewegen, 1990; Krout et al, 2002; Steriade, 1999). Clinical

evidence also implicates the importance of the ILn, midline, and MDn nuclei in arousal and related aspects of cognitive functioning. For example, following thalamic infarction caused by disruption of blood supply in the paramedian artery, which typically innervates the MDn, ILn and the dorsal internal medullary lamina (IML), patients suffer from decreased arousal and in extreme cases a 'coma vigil' or akinetic mutism (awake unresponsiveness), if disruption is bilateral. Patients may also suffer memory disturbances with perseveration and confabulation as prominent behavioural features. In addition, impulsive aggressive outbursts, loss of initiative, and a reported absence of spontaneous thoughts or mental activity are common in later stages of recovery (Schmahmann, 2003).

Animal lesion models have confirmed the involvement of the medial thalamus in memory tasks. Yet the previous two studies in this current research have provided clear evidence that differential memory deficits occur on different tasks following lesions to each of the AT, LT and MT thalamic aggregates. This empirical behavioural evidence suggests a functional role for each of these aggregates in different attributes of information processing. However, as previous conclusions suggest (e.g. Van der Werf et al, 2000; 2003), these memory deficits may have been secondary manifestations that were primarily the result of disruption to normal functioning in the prefrontal cortex (PFC). Furthermore as indicated in Chapter 6, these LT and MT aggregates in particular, are significantly interconnected with the PFC, which following lesions has been shown to impair the capacity for sustained attention, motivation and / or behavioural inhibition problems amongst other cognitive and behavioural deficits (Dias & Aggleton, 2000; Chudasama & Muir, 1997). The conclusions of Van der Werf et al regarding the MDn and ILn may not appear quite so likely now that double dissociations have been established across an array of behavioural tasks in the current research amongst the thalamic aggregates of interest in this thesis, yet it nevertheless is of interest to conduct an assessment of some type of attentional processing for the LT and MT thalamic aggregates.

As indicated in Chapter 6 the PFC areas can be separated into several regions by their distinct neural interconnections with sub-cortical structures, which imply their independent functioning in different information processes. Moreover it is proposed that the different PFC areas are particularly important at coordinating the lower-level sensory and motor processes, when the behaviour must be guided by internal states or intentions (Miller & Cohen, 2001). In humans, positron emission tomography (PET) suggests that differential regions of the PFC are involved in different aspects of attentional processes and executive functioning. The orbital frontal cortex is involved in selective attention, the dorsolateral and anterior cingulate cortices are involved in divided attention (Corbetta et al, 1991), and sustained attentional processing

involves frontal and parietal lobes (Pardo et al, 1990; also see Miller & Cohen, 2001 for a review of PFC function).

Several animal lesion studies also suggest that different regions of the PFC are involved in different aspects of attention and executive functioning. Delatour and Gisquet-Verrrier (2001) argue that the prelimbic-infralimbic cortical areas are involved in processes that support attentional mechanisms and behavioural flexibility. Other researchers have reported similar results using assessments of attention and response inhibition following lesions to the medial PFC (Birrell & Brown, 2000; Bussey et al, 1997; Dias & Aggleton, 2000; Granon et al, 1998; Granon & Poucet, 2000; Li & Shao, 1998; Ragozzino et al, 1998, 1999). Furthermore, it appears that the anterior cingulate cortex in particular is involved in response inhibition (Muir et al, 1996). Muir and colleagues reported dissociable effects of lesions to the dorsal PFC and ventral PFC in an assessment of attentional processes using a five-choice serial reaction time task, with dorsal PFC lesions causing more premature responding and ventral PFC lesions causing more perseverative responding.

Due to the prominent neural connections of the medial thalamic nuclei, especially the LT and MT aggregates, it is plausible that these regions may contribute to attentional processes and executive functioning too. In order to assess the involvement of the ILn in sensory attention, Burk and Mair (2001) directly assessed the effects of neurotoxic ILn lesions using a self-paced serial reaction time task. They reported that the ILn lesion group showed longer response latencies in the task but were unimpaired in response accuracy. Furthermore their intralaminar lesion group had no apparent deficits on the capacity to resist distraction or to respond when the stimulus salience was reduced. The authors concluded that connections between the ILn and lateral striatal regions were disrupted in this type of processing, as lateral striatal lesions had produced similar results in a previous experiment (Mair et al, 2000).

The functional contributions of other thalamic nuclei in attentional processing of rats have also been assessed. Chudasama and Muir (2001) assessed visual attention following lesions to the prelimbic (PL) cortical area and the AT, and MDn nuclei in rats in a five-choice serial reaction time task and a vigilance task. They reported dissociable deficits for PL and MDn lesions, whereby the PL rats perseverated with their responses whereas the MDn rats showed increased premature responding during the serial reaction time task. The AT lesion rats were unimpaired. In contrast to the serial reaction time task, both the MDn and AT lesion rats were unimpaired in the vigilance task, while the PL lesion rats showed impaired ability to distinguish signal and non-signal events (Chudasama & Muir, 2001). This evidence suggests

that MDn and PL cortex are involved in different aspects of attention, while the AT does not disrupt this type of sustained attention.

The present study was designed to test cognitive functioning associated with the PFC, namely sustained attention and response inhibition. In addition, further assessments of memory for temporal order were made using additional delays and the rats were also assessed in a familiarity versus novelty object recognition task. The first task of this third study assessed sustained attention and response inhibition of rats, using automated operant chambers. The sustained attention task (cf. Courtiere & Hardouin, 1997) requires the rat to maintain their attention long enough to detect, and react to, subtle variation in the brightness of a house light situated in the roof of the operant chamber. Initially a trial is started with 20s of darkness (a lever press during this period is recorded as a premature response error), and then the duration for illuminating the dim light is randomly varied between 4s through 8s (a lever press during this period is recorded as an anticipatory response error). During this random delay period of dim light the rat must sustain their attention in anticipation of a switch to the bright light, with a lever press during this period resulting in a reward. If the rat does not make a response during the trial it is recorded as an omission. Large medial PFC lesions, encompassing damage from precentral (Fr2) through to infralimbic (IL) cortical areas resulted in increased premature and anticipatory responses errors and omissions in responding during the trials (Broersen & Uylings, 1999; Broersen, 2000), while more limited damage to the anterior cingulate, PL and dorsal IL cortical areas resulted in increased premature responses and omissions in responding (Granon et al, 1998). Hippocampal lesion rats have also been assessed on the task demonstrating increased premature and anticipatory responses, but these deficits were attributed to a general behavioural disinhibition due to their increased levels of locomotor activity reported in the open field, rather than disruption in attentional processes per se. In the current experiment it was predicted that MT and LT rats might both exhibit impaired performance, including increased premature and anticipatory responses due to connections with the dorsal PFC and also more omissions in responding from the MT lesion due to the connections with the ventral PFC.

In the second task, all rats were assessed on memory for temporal order. The temporal order memory task was similar to that used in the first study with additional delays introduced between presentations of the two sets of objects. The additional delays in the temporal order memory task (5, 17 and 60 min) were introduced to determine whether shorter delays might also alter temporal order processing. The third task investigate familiarity versus novelty object recognition following a period of two hours, which was the same paradigm to that used in the

first study. This object recognition task was used to assess whether animals could continue to recognise familiar objects following the longest delay used in the temporal order memory task.

9.2 Materials and Methods

9.2.1 Subjects

As per the previous experiments, female hooded rats weighing between 180 and 220 gm at the beginning of pre-surgery training in the operant boxes were used as the subjects in this experiment. They were housed together and were food restricted as per previous details. All testing occurred between 1030 and 1530 hr at a rate of 6 sessions per week with one session per day. All protocols conformed to the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Animal Ethics Committee of the University of Canterbury.

9.2.2 Surgery

The general surgical procedure for this third set of rats was the same as that used in the first and second studies, other than the modifications outlined below. The lesions coordinates and NMDA infusion volumes for the MT rats were identical to those used in the first study, while the lesion coordinates and infusions volumes for the LT rats were identical to those used in the second study. These lesions coordinates and NMDA infusion volumes are outline in Table 12 below.

Sham lesions controls also received surgery but with no infusion as per the same coordinates and procedure used in the first experiment.

Table 12. Lesion coordinates for individual rat Bregma–Lambda (B-L) measurements and corresponding AP coordinates, as well as ML and DV coordinates, and NMDA Infusion Volumes for the Two Medial Thalamic Aggregates Assessed in the Present Study

	LT			MT	
	Two Ant sites		Post	Ant	Post
B-L distance for AP coordinates					
0.60-0.61 cm	-0.345		-0.385	0.365	-0.405
0.62-0.63 cm	-0.355		-0.395	-0.375	-0.415
0.64-0.66 cm	-0.365		-0.405	-0.385	-0.425
0.67-0.68 cm	-0.375		-0.415	-0.395	-0.435
ML	±0.130		±0.130	±0.000	±0.000
DV	-0.60	-0.56	-0.56	-0.560	-0.570
Volume μl	0.07	0.05	0.05	0.20	0.18

Abbreviations: Ant = anterior AP site, AP = anterior-posterior direction from bregma, DV = dorsal-ventral direction from dura, LT = lateral medial thalamic lesion, ML = medial-lateral direction from midline, Post = posterior AP site; PT = posteromedial thalamic lesion.

9.2.3 Histology

The histological procedure was the same as that previously used and the same criteria for inclusions and exclusions of rats in the behavioural analyses as per brain damage in the medial thalamus was maintained.

9.3 Sustained Attention (Vigilance) Task

9.3.1 Apparatus

Twelve operant chambers measuring approximately 28 x 20 x 23 cm were used. Each chamber contained a lever (2 cm long x 3 cm wide) positioned to the right side of the dipper dispenser and raised 8 to 10 cm above the floor. A light (25 watt bulb) was centered on the roof of each chamber, which delivered light of variable brightness. The reinforcement (diluted condensed milk: 1 x 395 ml can per 2L of cold water) was delivered at 0.12 ml per reinforcement via a mechanical dipper. The chambers were located in a darkened room and each chamber was itself enclosed in a sound-attenuating box with a ventilation fan at the rear that also helped to

mask extraneous sounds. The chambers were operated and data recorded using MED-PC programming and an IBM-compatible computer located in the adjoining control room.

9.3.2 Procedure

Prior to surgery, rats were familiarised to the operant boxes and trained on a fixed ratio 1 schedule using diluted condensed milk as the food reward (motivator). After 50 correct responses on each of two consecutive days, they were progressively trained with the visual detection task for 100 trials per session.

The inter-trial interval was 4s. Each trial began with the extension of the right-sided lever and a 20s delay of darkness. This was followed by the illumination of the light (3 lux) for a variable duration (preparatory period of 4.5s mean duration, range 3.0 – 6.0s), and then a switch to a brighter illumination (11 lux) for 2.0s duration. During this last 2.0s of the brighter light, if the rat responded with a lever press it was rewarded. A correct response (i.e. during the brighter light presentation) resulted in the delivery of the dipper with the condensed milk reward and the illumination of the dipper chamber for 4s before the lever was retracted and then a new trial began. An incorrect response (lever press outside the brightest period) or no response (omissions) thus resulted in the end of the trial and the lever was retracted. During the progressive training period, a longer duration for the brighter light (11 lux) was used (i.e. a 4.0s duration that was gradually reduced to the 2.0s duration), and also shorter periods of dim light (3 lux; i.e. a range of 1.0 – 4.0s) that were gradually increased to between 3.0 – 6.0s. The procedure for each trial was similar to the one used by Granon et al (1998) and is schematically detailed in Fig. 27.

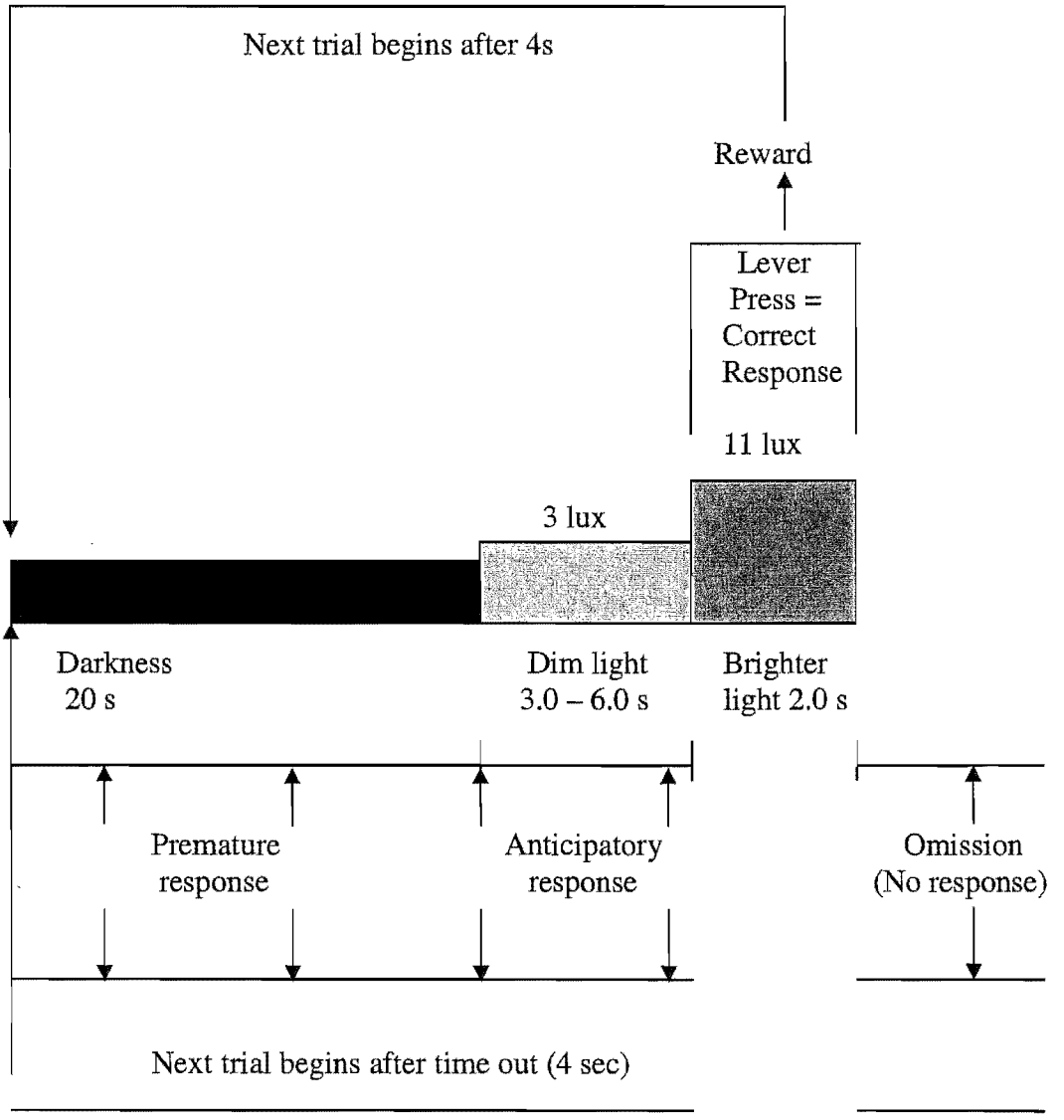

Fig. 27. Schematic diagram of the procedure for the sustained attention task in the operant boxes.

The behavioural criterion was initially set at an average of 65% correct across five consecutive sessions. However, following seven months of continuous training this criterion was reduced to above 50% correct averaged across five consecutive sessions.

Upon maintaining stable behaviour at this criterion, rats were matched for accuracy and randomly assigned to independent lesion groups for surgery. Half of the rats then went back into the operant box procedure following 10 days post-operative recovery for 15 sessions as per the pre-surgery procedure and then five sessions using a 1.5s brightness period. This reduction was used to assess change in stimulus duration. The other rats completed the temporal order memory and object recognition tasks before returning to the operant box procedure, 19 days following surgery. Of the 36 rats ran in this experiment only 25 rats reached and maintained the behavioural criterion in the operant boxes. The other 11 rats had completed training in the operant boxes but were not post-operative tested in this task, rather they were only tested in the temporal order memory and object recognition tasks.

9.4 Memory for Temporal Order

9.4.1 Apparatus

The boxes and the testing environment used in this experiment were the same as those used for the temporal order memory task from the first experiment (see Chapter 7). The objects used in this experiment were triplicates of weighted glass and plastic bottles, light bulbs, aluminium cans, and crockery ornaments (measuring between 120 cm and 230 cm high).

9.4.2 Procedure

The set-up and initial familiarization procedure were the same as the previous description in Chapter 7. The testing procedure was altered from the first experiment to incorporate the three different delays. Briefly, immediately after completion of the postoperative sustained attention testing, half of the rats were familiarised in the empty box for four daily 1-hr sessions and a final procedural familiarisation session on the fifth day as per the first study. On the next day, the rats received a 5 min study trial to explore a pair of identical objects (A), followed by either a 5, 17 or 60 min delay (delay order counterbalanced across rats and delay intervals), and then a second 5 min study trial to explore a second pair of

identical objects (object B). The rat was placed in the holding cage during the delay interval. On completion of the second study trial, the rat was placed in the holding cage for a 60 min delay, after which the test trial began. For the test trial, the rat was placed back in the box for a further 5 min, with a triplicate of object A and a triplicate of object B (positions counterbalanced across rats). The time spent exploring each object was recorded when the rat was 2 cm or closer and facing the object (climbing not counted). Then 48 hours later the study and test trials were repeated using different objects and another delay of 5, 17 or 60 min (counterbalanced across rats) between study trials, then 48 hours later the final repetition using the remaining objects and delay was conducted.

The other rats in the experiment were tested in the temporal order memory and object recognition tasks immediately following surgery (familiarisation in the empty boxes began five days post-operatively) and followed the same procedures described in this and the following section (9.6).

9.5 Memory for Familiar versus Novelty Object Recognition Task

The apparatus and procedure for this object recognition task were identical to that described in the first study (Chapter Seven).

9.6 Data Analysis

To investigate performance levels in the sustained attention / response inhibition task, differences between the three lesion groups were assessed using between-groups ANOVA for number of correct responses, premature responses (darkness errors), anticipatory response (dim light errors) and omissions (no response), separated into two blocks: sessions 1 – 15, bright light stimulus presented for 2.0s and sessions 16 – 20, bright light stimulus presented for 1.5s.

For the memory for temporal order task, one-way ANOVA and independent t-test against a mean of zero were used to compare group differences in preference for objects during the 5 min test trials for each of the different delays (5, 17, 60 min) and for preference levels across order of testing (i.e. day 1, 2, 3) irrespective of delay. Repeated measures ANOVA was used to analyze levels of exploration of the different objects during the different study trials and to assess minute-by-minute preference levels.

For the object recognition task, one-way ANOVA and independent t-test against a mean of zero were used to compare group differences in preference levels for the objects during the 5 min test trial and also for the first minute only in the test trial.

9.7 Results

9.7.1 Histology

The minimum and maximum extent of acceptable lesions for the LT and MT thalamic aggregates are shown in Fig. 28A and B (p. 186). As was the case in the first two studies, acceptable lesions needed to meet an arbitrary criterion of at least 50% damage to the intended aggregate and less than 50% damage to either of the alternate aggregates (the AT aggregate was included to be able to infer whether the lesions also selectively excluded this region). In all acceptable lesions, damage was relatively large in the target regions and unintended damage to other thalamic structures was relatively minor (Table 13 on p. 186). The slight adjustment made to the infusion volume for the LT aggregate increased the specificity of lesions for this group and was comparable to damage sustained to the LT aggregate for the second study (Chapter 8). Damage sustained in the MT aggregate was comparable, though slightly larger than damage sustained to the MT aggregate in the first study (Chapter 7). Three LT lesion rats were excluded. Two of these sustained sufficient damage to the LT aggregate but also had extensive damage in the MT aggregate (one of these rats was ranked 6th highest in premature responses of the 25 rats in total, the other rat was not assessed in sustained attention post-operative testing), while the other sustained too little damage in the LT aggregate. Two MT lesion rats were excluded because neither received sufficient damage to the intended aggregate.

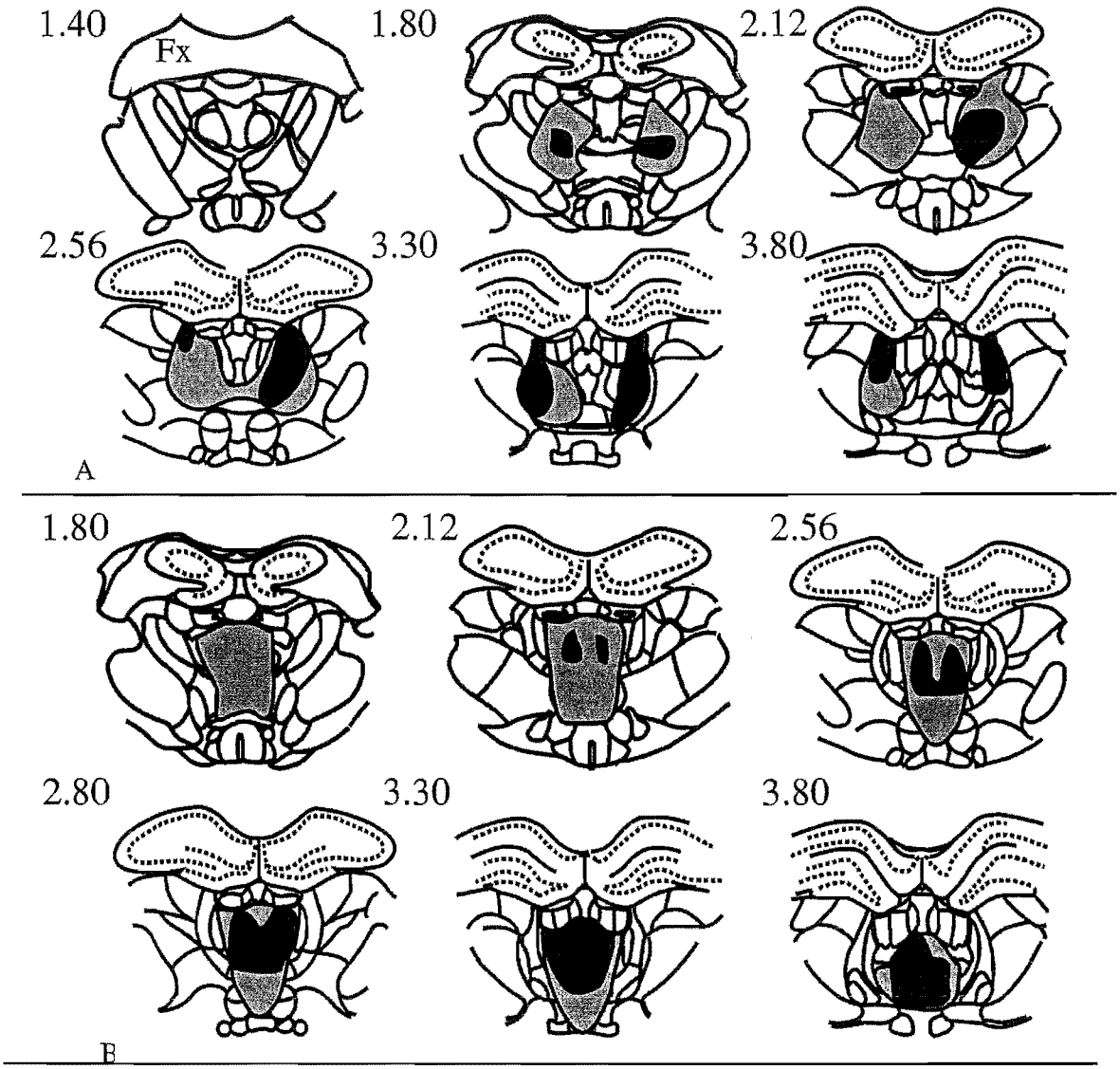

Figure 28. A series of coronal sections throughout the medial thalamus showing the area of cell loss with the smallest (*black*) and largest (*gray*) thalamic lesions. A: Lateral thalamic rats (LT). B: Posteromedial thalamic rats (MT). Coronal sections are adapted from Paxinos and Watson (1998) and coordinates are mm from bregma.

Table 13. Median (Range) of Bilateral Damage to the LT and MT Medial Thalamic Aggregates and Adjacent Medial Thalamic Nuclei (including the AT Medial Thalamic Aggregate) following micro-infusion of NMDA.

Region	CL	MDl/ MDpl	PC	rCeM	Total LT%	IMD	MDc	MDm	Total MT%	AD	AM	AV	Total AT%	IAM	LD	PT	PVA	PV/ PVP	Re/ Rh
Group																			
LT n= 10	90.9 (66.6-98.1)	90.7 (56.7-100)	59.3 (35.4-76.1)	16.4 (1.1-87.0)	71.4 (50.5-85.1)	0.0 (0.0-15.9)	38.7 (11.8-84.2)	12.7 (7.0-46.5)	19.8 (7.4-49.8)	3.2 (0.0-39.7)	7.0 (0.0-59.3)	5.5 (0.0-87.5)	5.1 (0.1-35.2)	0.2 (0.0-63.1)	1.0 (0.0-20.7	0.0 (0.0-22.1)	0.0 (0.0-19.7)	0.0 (0.0-3.7)	0.0 (0.0-44.1)
MT n= 10	0.0 (0.0-17.8)	0.2 (0.0-27.0)	14.3 (2.9-21.9)	74.5 (5.6-91.1)	14.7 (1.6-30.2)	100 (82.6-100)	85.1 (65.8-93.5)	74.2 (38.2-85.8)	79.2 (54.9-88.5)	1.5 (0.0-66.4)	17.0 (0.0-30.1)	0.0 (0.0-5.3)	6.6 (0.0-13.2)	32.9 (0.0-80.4)	0.0 (0.0-0.0)	29.6 (0.0-71.9)	37.4 (0.4-79.1)	99.7 (7.0-100)	0.0 (0.0-77.0)

Abbreviations:
AD= anterodorsal nucleus; AM= anteromedial nucleus; AV= anteroventral nucleus; CL= centrolateral nucleus; IAM= interanteromedial nucleus; IMD= intermediodorsal nucleus; LD= laterodorsal nucleus; MDc= central segment of mediodorsal nucleus; MDl= lateral segment of mediodorsal nucleus; MDm= medial segment of mediodorsal nucleus; MDpl= paralamellar segment of mediodorsal nucleus; PC= paracentral nucleus; PT= parataenial nucleus; PV/ PVP= paraventricular nucleus/ posterior paraventricular nucleus; PVA= anterior paraventricular nucleus; rCeM= rostral region of central medial nucleus; Re/ Rh= reunions nucleus/ rhomboid nucleus; Total AT%= total percent damage to anterior medial thalamic target; Total LT%= total percent damage to lateral medial thalamic target; Total MT%= total percent damage to posteromedial thalamic target.

9.7.2 Sustained Attention / Response Inhibition

Rats were pre-operatively trained in the sustained attention / response inhibition task, there was no significant differences between groups for any measure of responding in the task (Fs < 1.0) for correct performance, omissions and anticipatory responses and ($F_{2, 18} = 1.37$, $p > 0.28$) for premature responses.

Correct Performance (Lever Press during the Brighter Light). As shown in Fig. 29, the lever presses made during the 2.0s bright period of light, sessions 1 – 15 (correct responses) shows that the MT lesion rats had poorer performance than either the Control or LT lesion groups, although statistical analysis of the correct lever presses made indicated a non-significant effect of lesion, ($F_{2, 18} = 2.83$, $p < 0.09$). Further Newman Keuls post-hoc tests indicated that the MT lesion group made fewer correct responses than the LT ($p < 0.061$) and Control ($p > 0.22$) groups, which did also not differ ($p > 0.24$). There was a significant session effect, ($F_{14, 252} = 14.28$, $p < 0.0001$), indicating that responding during the bright light period improved across sessions of post-operative testing. There was no significant lesion x session interaction ($F < 1.0$). During sessions 16 – 20, the period of bright light stimulus was reduced to 1.5s, which resulted in poorer performance for correct responses across all groups. The effect of lesion was non-significant, ($F_{2, 18} = 2.71$, $p < 0.09$). Further post-hoc analysis indicated that the MT lesion group made fewer correct responses than the LT ($p < 0.072$) and Control ($p > 0.12$) groups, which did also not differ ($p > 0.47$). There was also no significant effect of session, ($F_{4, 72} = 2.43$, $p < 0.06$) and no significant lesion x session interaction ($F < 1.0$).

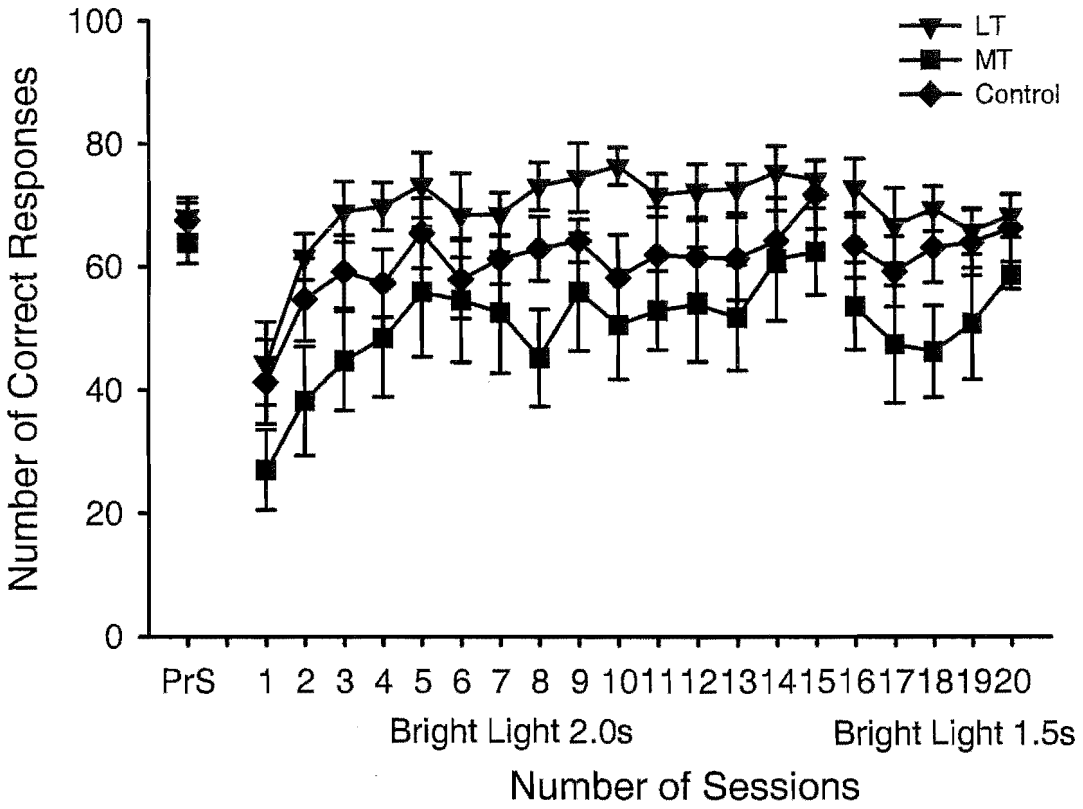

Fig. 29. The mean (±SEM) number of lever presses made during the brighter light duration (correct responses) for the three groups during each session of post-operative testing in the sustained attention task. PrS = pre-surgery levels of performance, Bright Light 2.0s = sessions 1 – 15 when the duration of bright light was set at 2.0s, Bright Light 1.5s = sessions 16 – 20 when the duration of bright light was set at 1.5s.

Premature Responses (Lever Presses During the 20s Dark Period). Analysis of the responses made during the 20s dark period (see Fig. 30) for the bright light stimulus at 2.0s (sessions 1 – 15), indicated an almost significant lesion effect, ($F_{2, 18} = 3.48$, $p < 0.053$). Further post hoc tests indicated that the LT group made significantly fewer premature responses than the MT group ($p < 0.04$) but did not differ to the Control group ($p > 0.11$), nor did the MT and Control groups differ ($p > 0.32$). There was a significant session effect, ($F_{14, 252} = 9.48$, $p < 0.0001$), indicating that premature responses were reduced as performance improved across post-operative sessions of testing, and a significant lesion x

session interaction, ($F_{28, 252} = 1.94, p < 0.004$). Post hoc comparisons revealed that this effect was due to the significantly reduced pre-mature lever presses made by the LT group compared to the MT group across sessions 2-6 and 8-10. Both the LT and Control groups and the MT and Control groups did not differ across sessions. When the bright light stimulus was reduced to 1.5s (sessions 16 – 20), dark period responses increased slightly for all groups. Statistical analysis indicated there was no significant lesion effect, ($F_{2, 18} = 1.95, p > 0.17$), session effect, ($F_{4, 72} = 1.76, p > 0.14$) or lesion x session interaction, ($F_{8, 72} = 1.37, p > 0.22$).

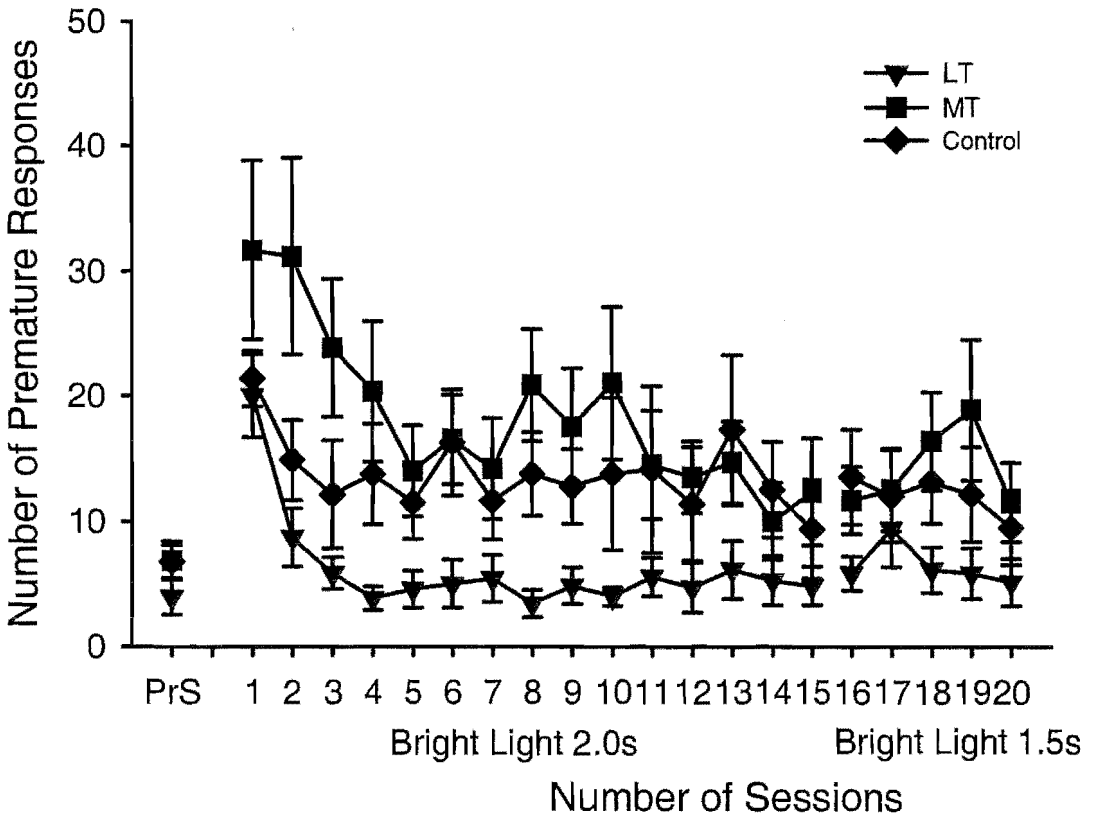

Fig. 30. The mean (±SEM) number of lever presses made during the 20s dark period (pre-mature responses) for the three lesion groups during each session of post-operative testing in the sustained attention task. See Fig. 29 for abbreviations.

Anticipatory Responses (Lever Presses During the Dim Light 3.0 – 6.0s). Analysis of the lever presses made during the random interval of dim light (see Fig. 31) for sessions 1 – 15 showed a significant session effect, ($F_{14, 252} = 3.63$, $p < 0.0001$) indicating fewer anticipatory responses as performance improved across sessions of post-operative testing. There was no effect of lesion, ($F < 1.0$) and no significant lesion x session interaction ($F < 1.0$). Furthermore as Fig. 31 shows, when the duration for the bright light stimulus period changed to 1.5s (sessions 16 – 20) the MT lesion group made more lever presses but the analysis showed that the increase in anticipatory responses was not significantly different to either the LT or the Control groups, ($F_{2, 18} = 2.43$, $p > 0.11$). There was also no significant session effect, ($F_{4, 72} = 1.42$, $p > 0.24$) or lesion x session interaction ($F_{8, 72} = 1.26$, $p > 0.28$).

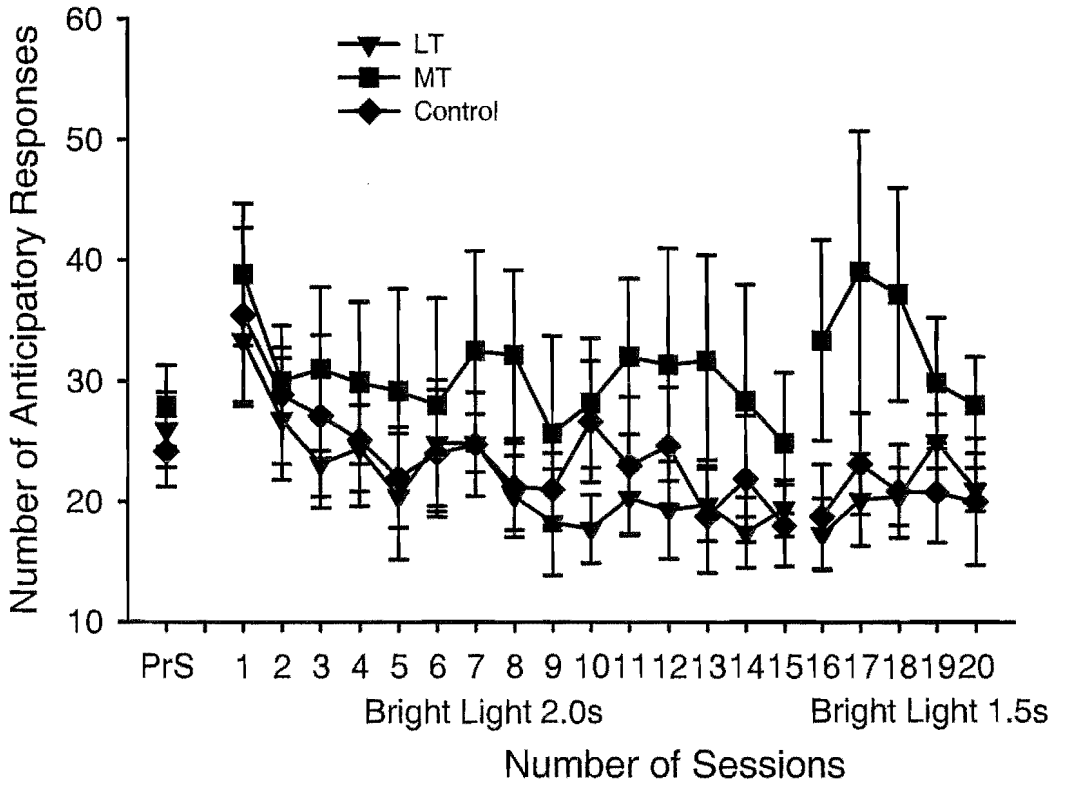

Fig. 31. The mean (±SEM) number of lever presses made during the dim light (3.0s – 6.0s) period (anticipatory responses) for the three lesion groups during each session of post-operative testing in the sustained attention task.

Omissions (No Responses During the Trial). As shown in Fig. 32, during sessions 1 – 15, there were no differences between groups for omissions. Statistical analysis confirmed that there was no lesion effect, ($F < 1.0$), no session effect, ($F_{14, 252} = 1.07$, $p > 0.39$) and no significant lesion x session interaction, ($F < 1.0$). During sessions 16 – 20, both LT and Control groups showed slightly poorer performance than the MT group, although analysis confirmed that there was no lesion effect ($F_{2, 18} = 2.55$, $p < 0.11$), no session effect, ($F_{4, 72} = 1.01$, $p < 0.41$) and no significant lesion x session interaction, ($F < 1.0$).

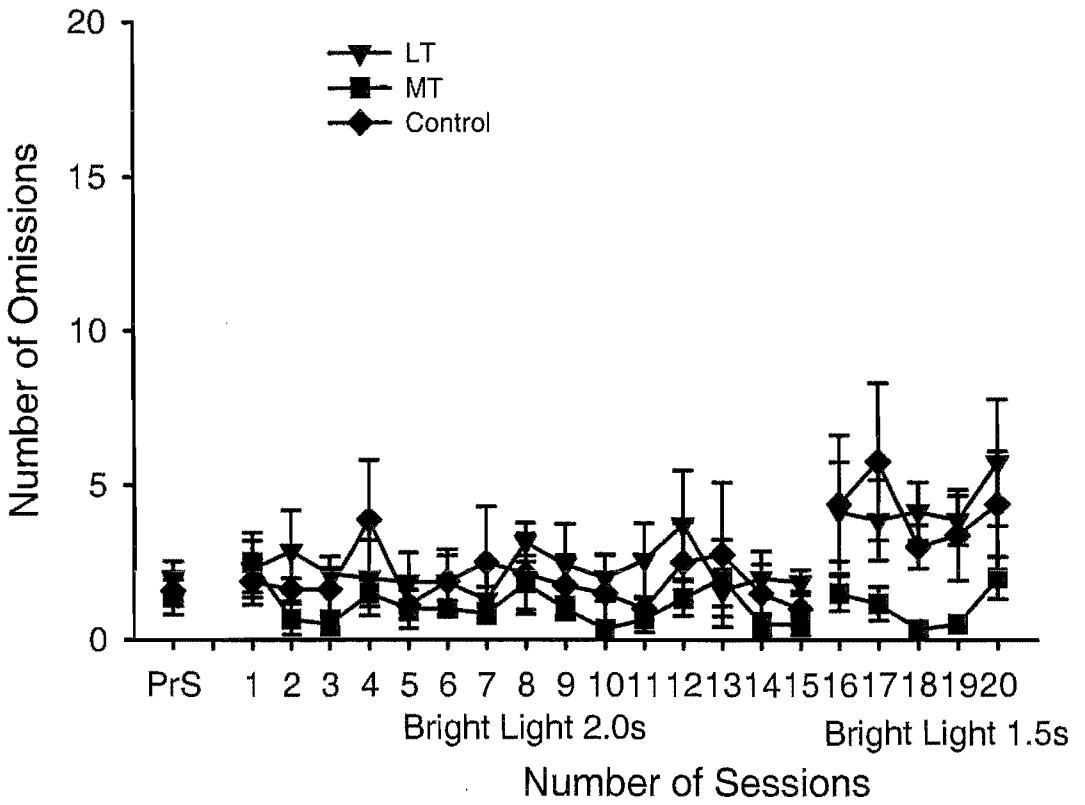

Fig. 32. The mean (±SEM) number of no responses made during a trial (omissions) for the three groups during each session of post-operative testing in the sustained attention.

9.7.3 Memory for the temporal order of two familiar objects

Preference for two different, but familiar, objects was observed during three different test trials employing different delays between the two study trials, namely 5 min, 17 min and 60 min. The delays and objects were randomised across rats and the three test sessions but will be presented here in numerical and alphabetical order, respectively for simplicity.

Analysis of 5 min delay between the two study trials. The average exploration time for the first identical pair of objects (A) in the first study trial was 27.61s and the exploration time for the second identical pair of objects (B) in the study trial one hour prior to the test trial was 22.00s. This difference was not significant, ($F < 1.0$). Average exploration times did not differ between groups, LT = 23.32s (SD = 7.21), MT = 26.48s (8.73), and Control = 24.56s (5.99), or vary systematically between groups across study phases, (group x study phase, $F < 1.0$). In the test trial, the same analysis of preference was used from the first study (Chapter 7). Briefly, the preference for the older of the two objects was assessed as a ratio score of the exploration time of the first familiar object (A) versus the exploration time of the second familiar object (B), divided by the total exploration time of both objects [(A-B)/(A+B)].

This analysis revealed no effect of lesion across preference ratios, ($F < 1.0$). Furthermore, differences did not emerge when each lesion group ratio was assessed by single sample t-test to determine whether it differed from chance preference. As Fig. 33 shows, the preference levels of the LT, MT and Control groups were not different to chance ($p > 0.24$, $p > 0.43$, $p > 0.17$, respectively).

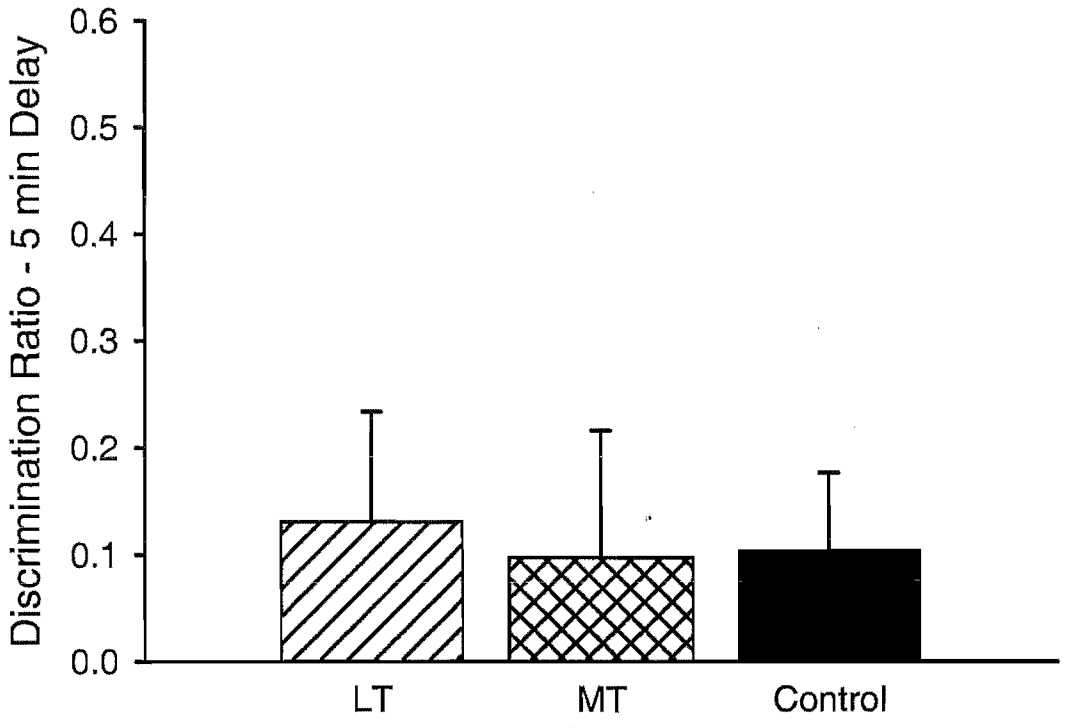

Fig. 33. Memory for temporal order of two objects following separate presentations of objects using a 5 min delay between study trials. No group showed significant preference compared to chance discrimination. Values show mean (±SEM) discrimination ratios during a choice test.

Analysis of 17 min delay between the two study trials. The average exploration time for the first identical pair of objects (C) in the first study trial was 31.90s and the exploration time for the second identical pair of objects (D) in the study trial one hour prior to the test trial was 22.33s. This difference was significant, ($F_{1,28} = 18.77$, $p < 0.0002$). Average exploration times did not differ between groups, LT = 24.64s (SD = 7.25) MT = 32.00s (10.93), and Control = 24.71s (6.82), or vary systematically between groups across study phases (group x study phase, $F_{2,28} = 2.13$, $p < 0.14$). In the test trial, there was no group effect of lesion across preference ratios, ($F_{2,29} = 1.22$, $p < 0.31$). Furthermore, differences did not emerge when each lesion group ratio was assessed by single sample t-

test to determine whether it differed from chance preference. As Fig. 34 shows, the preference level shown by the LT, MT and Control groups was not different to chance ($p >$ 0.06, $p > 0.46$, $p > .41$, respectively).

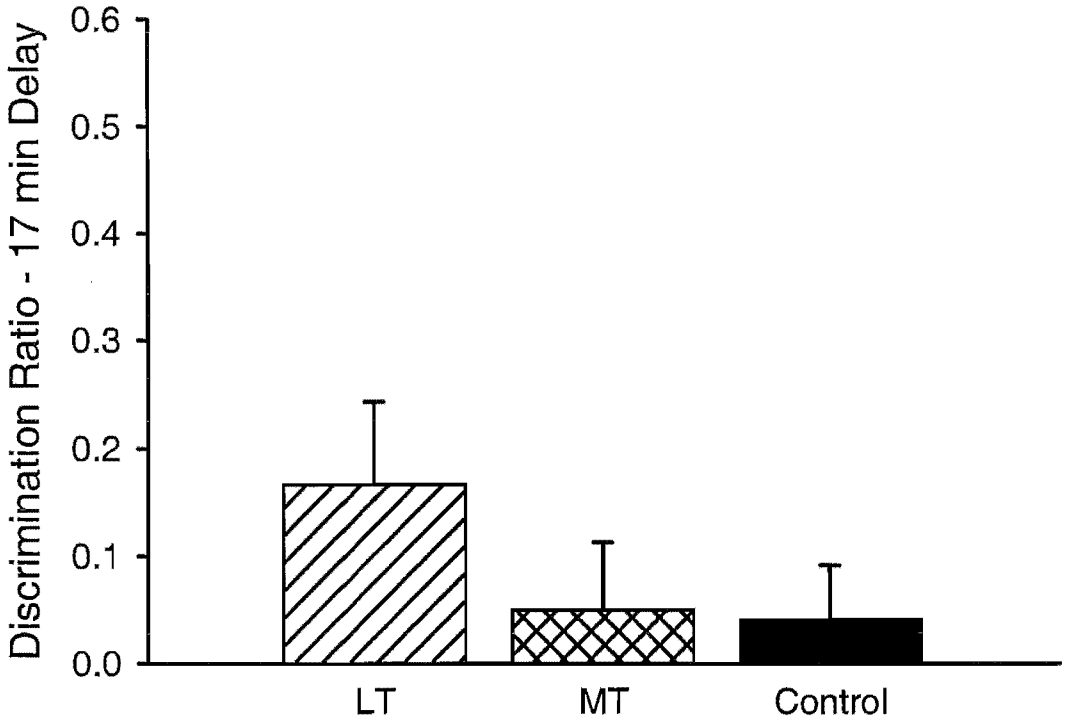

Fig. 34. Memory for temporal order of two objects following separate presentations of objects using a 17 min delay between study trials. No group showed significant preference compared to chance discrimination. Values show mean (±SEM) discrimination ratios during a choice test.

Analysis of 60 min delay between the two study trials. The average exploration time for the first identical pair of objects (E) in the first study trial was 25.89s and the exploration time for the second identical pair of objects (F) in the study trial one hour prior to the test trial was 24.01s. This difference was not significant, ($F < 1.0$). Average exploration times just failed to differ between groups, ($F_{2,29} = 3.14$, $p < 0.058$), with further post hoc comparisons indicating that the Control group spent less time looking at the objects 21.57s (SD = 4.63), than either the LT = 26.21s (SD = 7.50), or the MT = 27.07s (4.27) groups, but these differences just failed to reach significance, $p < 0.07$ and $p < 0.08$,

respectively. There was no significant lesion x study phase interaction, ($F < 1.0$). In the test trial, there was no group effect of lesion across preference ratios, ($F < 1.0$). Furthermore, differences did not emerge when each lesion group ratio was assessed by single sample t-test to determine whether it differed from chance. As Fig. 35 shows, the preference levels shown by the LT, MT and Control groups were not different to chance ($p > 0.58$, $p > 0.56$, $p > 0.23$, respectively).

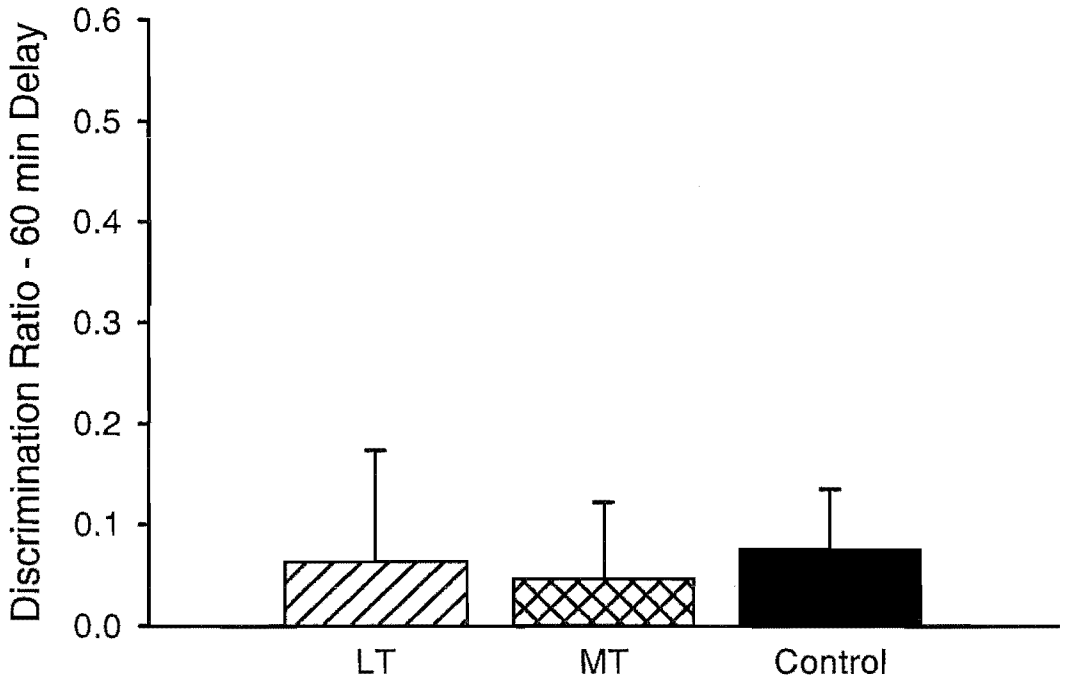

Fig. 35. Memory for temporal order of two familiar objects following separate presentations of objects using a 60 min delay between study trials. No group showed significant preference compared to chance. Values show mean (±SEM) discrimination ratios during a choice test.

Analysis of minute-by-minute preference ratios irrespective of delay for LT, MT or Control groups (see Fig. 36) demonstrated a significant effect of lesion during the second min of the test trials, ($F_{2,27} = 3.37$, $p < 0.05$). Further post hoc analysis indicated a significant difference in preference for the older object ($p < 0.042$) shown by the Control group (ratio = 0.35) compared to the MT group (ratio = -0.06); no other group differences emerged; Control and LT ($p > 0.13$) and LT and MT ($p > 0.31$). There were no significant effects of lesion for the first min ($F < 1.0$) or 3-5 min ($F < 1.0$). These last three minutes

were grouped together as many rats did not explore either object during these last minutes. Furthermore there was no difference in preference levels compared to chance preference, as measured by single-sample t-test. This result was due mainly to the extreme variability in object exploration within individual minutes of the test trials.

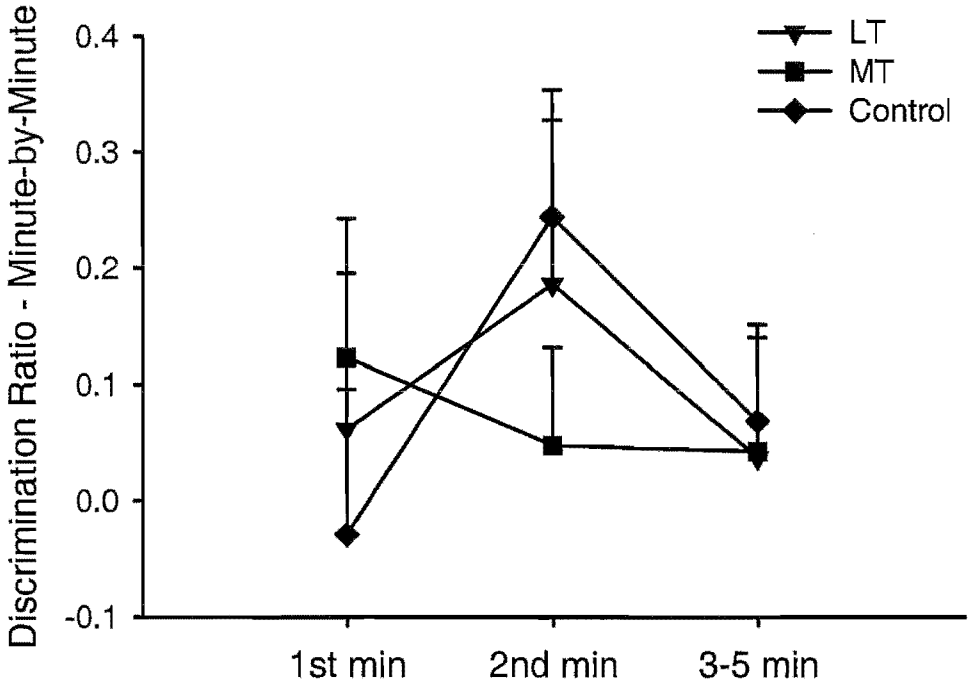

Fig. 36. Memory for temporal order shown by the three lesion groups across individual minutes of the test trials irrespective of delay. All preference ratios are not significantly different to chance levels. Values show mean (+SEM) discrimination ratios during a choice test.

Finally, the preference ratios were re-grouped by day of testing (day 1, 2, 3) irrespective of delay between study trials. Analysis of time spent exploring objects during test trials across days indicated no significant effect of lesion, ($F < 1.0$) day, ($F < 1.0$) or lesion x day interaction, ($F < 1.0$).

9.7.4 Memory for familiarity versus novelty object recognition

In this task, the test trial included one copy of an object (G), which the rat had previously explored during a study trial 2 hours prior to the test trial and a second object that was completely novel (H). In the 5-min study trial, analysis of the exploration time for the

object (G) revealed no differences between groups, ($F < 1.0$); LT = 33.32s (SD = 10.83), MT = 35.38s (13.78), and Control = 30.04s (7.95). In contrast to memory for temporal order, recognition memory, measured as total exploration time for the novel object verses total exploration time for the familiar object divided by total exploration time for both objects [(H–G)/(H+G)], was evident in all three groups, when compared to a mean of zero (p's < 0.02; Fig. 37). A one-way ANOVA revealed no clear difference between the groups, ($F_{2, 29} = 1.69$, $p > 0.2$).

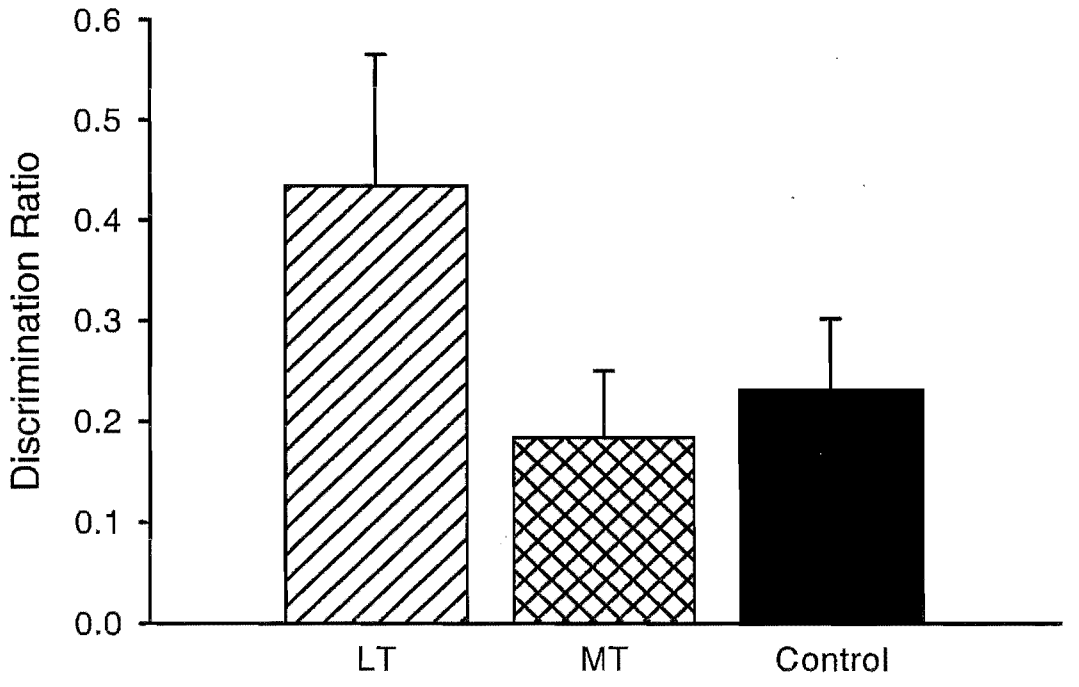

Fig. 37. Memory for familiarity versus novelty object recognition (two-hour retention delay); all groups preferred the novel (H) versus familiar (G) object (p's < 0.02 and above). Values show mean (±SEM) discrimination ratios during a choice test.

Additional analyses of the discrimination ratio for preference of the novel object over the familiar object during the first minute indicated mixed results of preference across the lesion groups. Only the LT group showed preference for the novel object, ($p < 0.01$) whereas the preference levels for both the MT and Control groups did not differ from chance, ($p > 0.40$ and $p > 0.92$, respectively).

9.8 Discussion

Studies in animals and humans of thalamic amnesia have implicated the intralaminar (ILn) and mediodorsal (MDn) thalamic nuclei in memory impairments as a result of disruption to the prefrontal cortex causing deficits in executive functioning. For example, in animal studies MDn and ILn lesions have resulted in perseverative responding, deficits in withholding spatial responses or changes in activity and exploration levels (Alexinsky, 2001; Burk & Mair, 2001; Hunt & Aggleton, 1991, 1998b). Similarly in the clinical literature damage in the MDn and ILn thalamic regions can alter attentional processes, motivation and / or arousal, and this damage can also result in a loss of the use of memory strategies (Van der Werf et al, 2000, 2003; Schmahmann, 2003).

Sustained Attention

In the present study, rats with lesions to the LT aggregate, which comprises the rostral ILn and lateral and paralamellar segments of the MDn, and MT aggregate, which comprises the remaining MDn, did not show impaired performance compared to the Control group on the sustained attention task, which has been shown to be sensitive to prefrontal cortex lesions. Furthermore the findings suggested that the LT aggregate performed better than both the MT and Control groups.

The lack of behavioural and cognitive evidence of prefrontal dysfunction following the MT or LT thalamic aggregate lesions is not completely consistent with recent conclusions that brain damage sustained in the midline, ILn, or MDn thalamic nuclei may lead to executive dysfunction, namely deficits in attention and planning with increasing apathy and disinhibition (Van der Werf et al, 2000, 2003). Although, interestingly the nature of the lesions produced in the current experimental rats, that is highly selective lesions to the medial thalamic targets of interest, is in accord with a recent proposal that suggests if damage is sustained in only one thalamic nucleus, this damage may be insufficient to produce a pronounced dysexecutive syndrome (Van der Werf et al, 2003).

The findings from the current experiment are also similar to previous research that has reported no deficits on a vigilance task following MDn lesions (Chudasama & Muir, 2001). In this task rats were required to detect a short flash of light (0.5s) presented directly

above the lever and were then required to press the lever within 3s of the flash of light. MDn lesion and AT lesion rats were not impaired in this task (Chudasama & Muir, 2001).

The sustained attention (vigilance) task used in the present study does not assess all types of attention processing, i.e. divided attention, and selective attention are not assessed in this sustained attention task. Therefore the current results can not be conclusive of all attentional processes. For example, in the serial reaction time attention tasks, which measure divided and selective attention to a greater degree than sustained attention, it has been reported that no deficits in performance occur following ILn lesions (Burk & Mair, 2001), although following lesions to the MDn, rats increased their premature responses (Chudasama & Muir, 2001). Therefore it may be concluded that in the sustained attention task at least lesions to the LT and MT do not produce deficits in attention. Moreover there was some evidence in the present study of an increased capacity for rats with LT lesions to withhold responding during the period of darkness when a lever press was recorded as a premature response.

Memory for Temporal Order

The findings for the temporal order memory task were somewhat unexpected. The first study (Chapter 7) implicated the LT and MT aggregates in memory for temporal order, as the rats with LT and MT lesions showed a lack of preference for either object, compared with AT and Control groups. The results of the present study have again demonstrated that following lesions to the LT and MT aggregates; both groups continue to show a lack of preference for either object, in spite of the shorter delays between study trials. This result for the LT and MT groups was expected as clinical evidence implicates lesions to these two regions produce deficits in temporal order memory (Shuren et al, 1997; Tanji et al, 2003), as does the first study in the current thesis. However, it was unexpected that the Control group was also impaired across all delays in the temporal order task.

A comparison of the findings between the first study (Chapter 7) and this current study may provide a suitable explanation for the unexpected results. The amount of exploration towards the objects in both study and test trials shown by the rats during the first study is substantially greater than that shown by the rats in the current study. In the first study all rats showed exploration times during the study trials that averaged 43s but

during the current study average exploration times during the study trials across delays only averaged 26s. It may be concluded then that the greater and more consistent levels of exploration shown by the rats in the first study allowed them adequate time to gain familiarity with the two objects, whereas in the current study the typically low and variable levels of exploration shown by the rats did not allow them adequate time to get adequately familiar with the objects. Therefore it can be concluded that the results of the first study assessing memory for temporal order are more reliable, but the results of the current study are too variable to produce clear results.

The reduced levels of exploration shown by the rats in the current study may reflect differences in pre-surgery training paradigms. For example, the current rats were pre-trained in operant boxes in the dark, which require very little mobility, whereas the rats in the first study were pre-trained in a radial maze task in the light, which requires high levels of mobility and exploration. Nevertheless, there were no substantial increases in exploration levels shown by the current rats across days of testing. Thus it can only be concluded from the current study of memory for temporal order that the rats did not allow themselves sufficient levels of exploration of the objects in both study and test trials to be able to indicate a preference for one of the objects presented.

Memory for Familiar versus Novel Objects

In the final task of familiarity versus novelty object recognition, the exploration levels of the objects in both study and test trials for all lesion groups continued to be low. In the object recognition task, however, all rats were able to distinguish the novel from the familiar object following the two-hour retention delay, indicating that they were able to remember objects over delay periods as they had also shown a capacity to do in the first study (Chapter 7). This finding further confirms that the results of the memory for temporal order task are not the result of rats in the current study failing to recognise the familiar objects.

Conclusions

Thus it can be concluded from the current findings that the effects of damaging the LT and MT thalamic nuclei does not necessarily caused a generalized impairment of

memory due to the primary disruption to prefrontal cortex sensitive tasks, although in order to be more conclusive about memory for temporal order deficits, it will be important to devise a task that shows more robust findings across groups of rats.

The following chapter is the final chapter of the dissertation and includes a general discussion of the behavioural contributions of the three studies (Chapters 7, 8 and 9) to the present theoretical interpretations of the neural basis of diencephalic amnesia.

Chapter 10

General Discussion and Conclusions

10.1 General Contributions

The current research investigated the neural basis of thalamic amnesia. This research adopted a new approach to this problem, by investigating whether each of the medial thalamic nuclei are involved in specific attributes of memory, in accord with the Attribute Memory Model proposed by Kesner (1998). This approach has generated novel findings to the contentious debate over the contributions of different medial thalamic regions.

The current research began by identifying the prominent neural connections of the medial thalamus (Chapter 6). This first step was essential in order to specify the commonalities and differences amongst the prominent neural connections of the medial thalamic nuclei. Advances in tracing techniques continue to provide greater understanding about the neural connections of the entire brain. This re-assessment identified several common groupings of nuclei that appear to be relatively independent of one another, namely a conventional aggregate (the anterior thalamic nuclei, AT) and at least two non-conventional aggregates (the lateral thalamic nuclei, LT and the posteromedial thalamic nuclei, MT). The latter two aggregates are non-conventional in the sense that the lateral MDn is aggregated with the rostral ILn. It is more conventional for lesions studies to exclude the lateral MD from ILn considerations or include the lateral MDn with the remaining MDn nuclei, although some monkey studies focus on the midline MDn nuclei (e.g. Gaffan & Parker, 2000). This re-alignment led to the hypotheses that each of the independent medial thalamic aggregates is a functional component within a neural circuit considered responsible for specific forms, or attributes, of memory. These hypotheses were confirmed in the current research when suitable behavioural tasks were included that could readily assess the specific memory attributes of interest. Therefore the behavioural

evidence suggests that each of the medial thalamic aggregates offer specific contributions to different attributes of memory and, moreover, these functions are dissociable from one another. Thus this approach may lead to further understanding of the neural basis for thalamic amnesia and memory processes of the brain.

Given the widely known difficulties over the lack of highly selective damage to separate medial thalamic nuclei, due to the small size, close proximity and complexity of the nuclei, it was important to develop an accurate method of causing highly selective neurotoxic lesions. It was also important to provide evaluations of damage sustained to the target and adjacent medial thalamic structures.

This PhD research has been successful in developing highly selective lesions to the medial thalamic aggregates while causing minimal damage to other target and adjacent medial thalamic structures, although it is impossible to avoid some additional damage to other medial thalamic nuclei using the current lesion techniques available. Therefore, it is probable that the behavioural evidence gathered, especially the double dissociations and the conclusions drawn from the behavioural tasks assessing the involvement of the medial thalamus in different aspects of memory, is highly reliable.

In summary, this general discussion will assess what specific contributions have been made from the current research with regard to our knowledge about the neural basis of memory related to the medial thalamus as well as suggestions regarding directions for future research. Some of the main issues addressed in this thesis are revisited in light of the behavioural findings that were revealed. A re-interpretation is offered about the neural basis of some of the deficits associated with thalamic amnesia.

10.2 Behavioural Contributions of the Current Research

Determining the neural basis of thalamic amnesia has by and large been hindered by the lack of clear dissociations regarding brain damage in specific nuclei and selective impairments on memory tasks. This study provided the first direct comparison across different memory tasks of brain damage to all three medial thalamic aggregates. The fundamental behavioural contribution associated with the current research was the ability to reveal double dissociations of memory processes amongst the identified independent medial thalamic target aggregates. These double dissociations in memory processing

demonstrated by the rats showed that only damage to the MT aggregate produces deficits in a magnitude for reward value task, which was dissociated from the finding that only damage to the AT aggregate produces deficits in spatial memory tasks, which was further dissociated from the finding that only damage to the LT aggregate produces deficits in an egocentric response task. Given the time restraints in this thesis, future experiments in our laboratory will study MT lesion effects on egocentric response tasks, but it is suggested that no deficits will be found after these lesions. These double dissociations in specific forms of memory were highlighted because the re-interpretation of the prominent neural connections of the medial thalamus led to the proposal that attributes of memory associated with each of the aggregates of thalamic nuclei could be made. This proposal was based on the notion that these aggregates each form functional components of independent neural circuits that are already associated with different memory processes in the current literature. Although the current proposal of thalamic involvement in neural circuits associated with memory stems from and overlaps with the proposals of Aggleton and Brown (1999), Mair et al, (2001), Van der Werf et al, (2002) and Gaffan et al (1993). The strengths of the current research were that clean, within-experimental dissociations were observed, the nature of those dissociations, and the consequential advance in our understanding of the neural basis of diencephalic amnesia.

Additional evidence in the current behavioural findings indicated that deficits in memory for temporal order were associated with damage to both the LT aggregate and the MT aggregate, but not the AT aggregate, suggesting a role for these two former thalamic aggregates in context based memory. In addition this evidence may also illustrate the unique contribution of the AT aggregate to spatial based memory. Moreover the lack of deficits shown by the LT and MT aggregates during performance in the sustained attention / response inhibition task further suggests that damage to these two regions does not necessarily disrupt some forms of non-memorial cognitive functioning that is sensitive to prefrontal cortex injury.

These findings provide an explanation for the variability in deficits both in animal lesion studies and, in particular, across human thalamic amnesic cases where there is variability in the deficits observed and more uncertainty in the nature and extent of brain injury (Schmahmann, 2003). The selectivity of the anterior ILN lesion effects displayed

across the memory tasks used here supports the recent proposal that these structures are involved in selective cognitive functions (Van der Werf, et al 2000). In contrast, the current findings do not support the view that the ILn or MDn are responsible for a generalised pattern of memory impairments (Gaffan & Parker, 2000; Mair et al, 1998) or that disruption to the AT is primarily responsible for diencephalic amnesia (Van der Werf et al, 2000, 2003; and as outlined in Chapter 4).

10.3 Theoretical Contributions of the Current Research

Both clinical and animal evidence have previously indicated that the structures of the medial thalamus contribute in some way to the functions of memory processing. This section begins with a brief summary of the conclusions to date. First it deals with the clinical evidence, which is followed by a brief summary of the animal evidence and then offers some speculative re-interpretation of the neural basis of these thalamic amnesic memory deficits in light of the current behavioural contributions.

The clinical evidence typically implicates damage to the mammillothalamic tract (MMT) and / or disruption to the anterior thalamic nucleus (AT) as being responsible for the amnesic syndrome associated of thalamic amnesia, and that this amnesia is similar to that produced following hippocampus / medial temporal lobe damage (Van der Werf et al, 2000, 2003). For example, Aggleton and Brown (1999) proposed that damage to part of an extended hippocampal system, comprising the hippocampus, fornix, mammillary bodies and anterior thalamic nuclei and for which the MMT is a major fibre tract, is a common feature of anterograde amnesia.

Memory deficits are also apparent in human patients following damage sustained to the MDn, ILn or midline nuclei, but these memory deficits are considered to be due to disruption of associated pathways projecting to the PFC and thus may be distinct from the episodic memory deficits attributed to damage in the MMT or AT in cases of thalamic amnesia. That is, the impairments to memory following damage to the MDn or ILn are considered by some to be a secondary consequence of disruptions in attentional, motivational or arousal processes and / or executive functioning of the PFC of the brain (Schmahmann, 2003; Van der Werf et al, 2000, 2002, 2003). In some clinical reports it is

noted that selective damage to the anterior thalamic region can also produce profound anterograde amnesic deficits in conjunction with deficits in some executive functions. For example, Ghika-Schmid and Bogusslavsky (2000) reported 12 clinical cases of anterograde amnesia and executive functioning deficits such as difficulties in programming motor sequences and an increased sensitivity to interference following damage restricted to the AT, MMT and anterior part of the internal medullary lamina (IML). More recently, Van der Werf et al (2003) have proposed that deficits in executive functioning and complex attentional processes can not be attributed to a specific structure. Rather they proposed that simple attentional deficits seem to be a general trait of thalamic lesion, while damage to several structures of the medial thalamic nuclei, including the MDn, ILn, and midline nuclei, accompany executive dysfunction. They also suggest that damage to the ILn will result in complex attentional deficits.

These clinical assessments of memory impairments that are based on damage in the thalamus resulting from infarcts, ischemia, and haemorrhage reflect damage that is not limited to just one nucleus or grouping of nuclei in the medial thalamus. With the broad range of deficits associated with thalamic brain injury it seems very unlikely that one specific region or fibre pathway of the medial thalamus is responsible for the degree or range of memory and other cognitive deficits observed in thalamic amnesics. It is evident that further investigations are needed to clarify the functional contributions of the medial thalamic nuclei in order to understand the consequences of disruptions caused by this brain injury.

We have already seen that animal lesion models of thalamic amnesia, using rodents especially and also monkeys, have confirmed the importance of the medial thalamus in memory. For example, the AT, ILn and MDn have all in turn been implicated in episodic-like memory processing (Aggleton & Brown, 1999; Gaffan & Parker, 2000; Mair et al, 1998; Burk & Mair, 1998, 2003). Furthermore, both the ILn and MDn have been implicated in memory impairments due to deficits associated with perseverative strategies, a reluctance to make a choice, deficits in arousal and / or cognitive awareness and more general dysexecutive functioning (Alexinsky, 2001; Burk & Mair, 1998; Hunt & Aggleton, 1998; Mair et al, 1998). In many ways the empirical evidence established in both the clinical and animal settings mirror one another. The conclusions drawn from the evidence

to date have been substantial and timely, especially with regard to the acknowledged role the AT contributes to episodic declarative memory, as part of an extended hippocampal memory circuit, in both humans and animals (Aggleton & Brown, 1999).

Nevertheless the neural basis of thalamic amnesia remains contentious, due mainly to the lack of any specific forms of memory deficits associated with the ILn and MDn nuclei. As mentioned above, in order to determine the neural basis of thalamic amnesia the current research hypotheses were driven by the proposal of Aggleton and Brown (1999) that the AT is a nodal point in a circuit involved in processing episodic declarative memory. Yet other researchers have suggested the functional involvement of the ILn and MDn within circuits involved in different aspects of learning and memory (Burk & Mair, 1998; Gaffan et al, 1993; Gaffan & Parker, 2000; Mair et al, 2001; Porter et al, 2001; Van der Werf et al, 2002). Mair and colleagues have specifically focused on the ILn and assessed deficits to this region across a comprehensive range of tasks. They have raised the profile of the ILn within memory processes and suggest that only extensive damage, which extends across the full extent of the ILn, produces comparable deficits in rats to those observed in diencephalic amnesics. On the other hand, Gaffan and colleagues have emphasized the importance of the medial magnocellular MDn to diencephalic amnesia and suggest that the prominent interconnections between the MDn and the prefrontal cortex provide an explanation for diencephalic amnesia, as the damage in the MDn results in disruptions to normal functioning of the PFC (Gaffan & Parker, 2000). Therefore with these conflicting theories there has thus far been little clarity or consensus as to which nuclei are pre-eminent in diencephalic amnesia or their specific contribution. For example, in the recent study of AT deficits in spatial memory tasks, Mair and colleagues (Mair et al, 2003) suggested that the AT may also contribute a part in addition to the ILn influence on general memory processes.

Thus the current behavioural contributions to the study of diencephalic amnesia offer another, and perhaps more encompassing theoretical perspective. The current findings reconfirm the current proposals of the AT involvement in an extended hippocampal system which contributes to spatial memory processes in rats and episodic declarative memory in humans (Aggleton & Brown, 1999). Furthermore the profound memory impairments demonstrated by the rats with AT lesions that were selective to the attribute of spatial

memory reinforces the selective nature of the memory deficits associated with this aggregate of nuclei. Thus damage to the AT alone may not explain the variability of memory deficits experienced amongst clinical cases of diencephalic amnesia.

Therefore the proposed theoretical analysis of diencephalic amnesia provides an alternative theory that also implicates the other medial thalamic aggregates, namely the LT and MT in specific attributes of memory. It is important to note that other researcher have also offered alternative proposals to the functional contributions of the MDn in declarative memory processes. For example, Aggleton and Brown (1999) suggest the MDn contribute to familiarity-based recognition memory, but as previously indicated, this proposal has meet with some disagreement.

During the current research, Kesner's (1998) Multiple Attributes of Memory Model provided the basis for selecting some of behavioural tasks used, especially in relation to the LT and MT thalamic aggregates, in order to test the hypotheses that these independent thalamic aggregates each contribute to different attributes of memory. The behavioural tasks used by Kesner and colleagues (DeCoteau et al, 1999; Kesner & Williams, 1995; Ragozzino & Kesner, 1999, 2001) provided the opportunity to compare the effects on performance of lesions to the medial thalamic nuclei with previous deficits reported from other researchers following lesions to the lateral and dorsal PFC, dorsal striatum and the amygdala.

As the current re-analysis of the prominent neural connections of the MT indicated this region is linked with the amygdala, lateral and medial PFC and the ventral striatum. Previous evidence in animal work has implicated the amygdala in a neural circuit that processes affect / reward value (Kesner, 1998) or stimulus-reward type associations (Gaffan et al, 1993; McDonald & White, 1993). The current behavioural findings also produced deficits in processing of reward value in a task that is sensitive to amygdala lesions (Kesner & Williams, 1995). Thus this current empirical evidence suggests the importance of the MT aggregate of medial thalamic nuclei to memory processes associated with an amygdala-based memory system. This re-interpretation consequently provides a different perspective on the functional role of the posteromedial thalamic nuclei, which are interconnected with the amygdala, in diencephalic amnesia.

In contrast, the re-interpretation of the prominent neural connections of the LT aggregate indicate that it is linked with the dorsal striatum and pallidum, and the dorsal PFC. Previous evidence in animal research implicates the dorsal striatum and dorsal PFC in a circuit that processes response information (Kesner, 1998), stimulus-response associations (McDonald & White, 1993, 2002) and memory for motor responses (Kesner, 2000; Ragozzino & Kesner, 2001). The current behavioural findings also provided evidence that lesions to the LT aggregate disrupt egocentric response memory processes in a task that has been shown to be sensitive to lesions in the dorsal PFC (Ragozzino & Kesner, 2001) but these LT lesion rats were unimpaired in spatial memory processes. Thus this current empirical evidence suggests the importance of the LT aggregate of medial thalamic nuclei to memory processes associated with a dorsal striatum-based memory system. This re-interpretation of the involvement of the LT aggregate in memory consequently provides a different perspective on the functional role of the rostral ILn and lateral and paralamellar segments of the MDn, which are interconnected with the dorsal striatum and dorsal PFC, in diencephalic amnesia.

It is worthwhile, then, to re-evaluate some of the reports of clinical cases of thalamic amnesia in light of the proposals that the medial thalamus is involved in specific attributes of memory.

That the MT aggregate produced deficits in memory for reward magnitude (affect), which is in accord with previous animal evidence showing deficits in a similar task following lesions to the amygdala and lateral prefrontal cortex (Kesner & Williams, 1995; Raggozzino & Kesner, 1999) suggests that these two regions operate together processing similar information related to reward-value memory. In non-human primates, lesion damage to the amygdala and medial magnocellular mediodorsal nucleus also produces deficits in reward value memory processes (Gaffan et al, 1990, 1993). Furthermore amygdala damage in non-human primates produces changes in emotional and social behaviour (Aggleton, 1993). In the clinical literature patients with Urbach-Wiethe disease, which produces selective but substantial damage to the amygdaloid region demonstrate little change to cognitive functions but substantial deficits emotionally (Adolphs et al, 1997; Markowitsch et al, 1994, 2003) and deficits in face recognition and impaired processing of emotional facial expressions (Adolphs et al, 2000; Adolphs & Tranel, 2004).

Furthermore, Markowitsch et al (1994) showed using PET scanning that there was an overall decrease in glucose hypometabolism of patients with Urbach-Wiethe disease compared to age-matched controls and that the thalamus and cingulum were most severely reduced, which they attributed to these regions prominent interconnections with the amygdala via the dorsal and ventral amygdalofugal pathways.

Thus in light of the current behavioural findings and the above examples of interactions between the MDn and amygdala, it may be possible to re-attribute the emotional deficits displayed by amnesic Korsakoff syndrome patients to a specific deficit in processing affect memory, as these patients sustain substantial atrophy of the MDn (Harding et al, 2000). For example, KS patients display deficits in affective judgements (Brand et al, 2003), impaired processing of affective prosody (Snitz & Daum, 2003) and impaired recall of emotionally related autobiographical memories, especially those associated with negative affect, for example, pain (Daum et al, 1996). Furthermore in clinical reports of other aetiologies of thalamic amnesia, which have caused damage in the MDn, patients have been described with altered personality and mood and changes in social skills. For example, Benke et al (2002) reported mania following bilateral MDn infarcts in a patient. The causes of these emotional and affect-based problems related to diencephalic amnesia are normally attributed to disruption in the connections to the PFC. However, instead the causes of these deficits in emotional behaviour and impaired affective judgements may be the result of disruption to the wider neural network of MDn connections, particularly the amygdala and lateral PFC circuit involved in affect memory processes (Kesner, 1998).

The LT aggregate produced deficits in memory for egocentric response, which is similar to previous animal evidence following lesions to the dorsal prefrontal cortex (Kesner et al, 1996; Raggozzino & Kesner, 2001). The current evidence is also consistent with notion that stimulus-response type associations are attributed to the dorsal striatum (Adams et al, 2001; Kesner et al, 1993; McDonald & White, 1993). A re-interpretation of the clinical evidence following thalamic damage could suggest that some of the memory deficits suffered by individual cases of thalamic amnesia could be due to disruption of the LT and its contribution to a neural circuit involved in egocentric response. For example, Holdstock et al (1999) reported deficits in egocentric information processing for KS

patients, who sustain substantial atrophy in the medial thalamus (Harding et al, 2000). Furthermore one MTL amnesic in the report of Holdstock and colleagues, also had deficits in egocentric processing and it was reported from the MRI scan that this patient had enlarged lateral and third ventricle spaces, which the authors suggested could be indicative of thalamic atrophy. The current behavioural findings would suggest a role of the ILn in these deficits of egocentric information processing.

Other researchers have demonstrated deficits in implicit memory processing using a serial reaction time task with thalamic infarct patients who sustained lesions involving the territory of the paramedian and polar thalamic arteries, namely the IML, MMT, MDn, ILn, and ventrolateral nuclei (Exner et al, 2001). Exner and colleagues reported that the deficits in performance of the thalamic infarct group were similar to those deficits shown by basal ganglia damaged patients in measures of attentional performance and general psychomotor processing speed. Differences emerged between the two patient groups in the learning and memory of the visual association task. The thalamic infarct patients had greater difficulties than the basal ganglia subjects in accomplishing the task. Moreover the extent of damage in the thalamus correlated with learning and memory deficits. The authors attributed the deficits to strong interconnections between the thalamus and the limbic system (Exner et al, 2001). However, in light of the current evidence suggesting a role for the ILn in egocentric response memory, the findings of Exner and colleagues could be attributed to disruptions in processing response memory attributes.

Thus it appears that the current proposals of the specific involvement of the medial thalamic nuclei in different attributes of memory associated with diencephalic amnesia provide an excellent beginning for an alternative interpretation of neuropsychological deficits. It is important to continue with further assessments of the contributions of the medial thalamic nuclei to clearly specific attributes of memory in both animal models and clinical assessments of thalamic amnesic patients. With regard to clinical assessments more comprehensive assessments using memory tests that are able to tease out certain and specific attributes of memory are required in patients across the range of aetiologies associated with diencephalic amnesia. It is proposed that the current re-interpretation may provide an initial framework for more accurate assessments of the capabilities of thalamic

amnesics, which could aid with understanding and could offer more effective treatment and behavioural therapies for diencephalic amnesics and their families.

Are all of these medial thalamic aggregates involved in declarative memory? As indicated the hypotheses of the current research were driven by previous theories of thalamic involvement in neural circuits considered responsible for memory and the interpretations of neural connections positioned these thalamic aggregates within multiple memory systems models. Perhaps the most relevant theory to the current research is that of the Multiple Attributes Model of Memory proposed by Kesner (1998) but this Multiple Attribute Model of Memory processes does not account for the contributions of medial thalamic nuclei in memory. To re-iterate Kesner's theory that was described in Chapter 3, the fundamental basis of Kesner's multiple attribute theory of memory is that the hippocampus in itself does not process all aspects of event-based memory (akin to episodic declarative memory), but rather only those events that include the attributes of time and space, while other brain structures process other attributes of memory, for example the amygdala is involved in affect, the caudate is involved in response, and the perirhinal and extra-striate cortices are involved in attributes of memory related to the senses (such as object recognition). Furthermore Kesner's attribute memory model proposes that a different knowledge-based memory system is more akin to semantic declarative memory and is involved with processing different aspects of information related to attributes of memory. For example, it is proposed that this knowledge-based system is involved with more permanent representations of previously stored information related to the specific attributes in long-term memory (i.e. one's general knowledge of the world).

Therefore despite Kesner's theory offering a credible alternative to how the brain is involved with memory, the theory does not incorporate the thalamus. Thus, it is now proposed in light of the empirical findings of this research that the Multiple Attribute Memory Model be revised to include the thalamus. In particular the relatively independent medial thalamic aggregates thus far identified in this thesis that appear to be functional components of the circuits identified to be involved in processing multiple attributes of memory. Furthermore other multiple memory system theories (Eichenbaum & Cohen,

2001; McDonald & White, 2002; Squire, 1992) also need to be adapted to include the contributions of the medial thalamic nuclei to memory.

10.4 Neurobiological Contributions of the Current Research

As indicated in this thesis the medial thalamic aggregates are proposed to be involved in different memory circuits, in the following discussion other relevant issues associated with the role of the medial thalamus in memory processes are briefly considered.

Some researchers have suggested that the identification of the head direction (HD) cells in certain regions of the brain, for example the AT, the mammillary bodies, and the hippocampal formation suggests that these HD cells are related to spatial memory processing, and further confirm the importance of these structures to spatial memory processing in animals (Sharp et al, 2001). Head direction (HD) cells, that is cells that fire when the head of the rat points in a certain horizontal position enabling it to gain a sense of its direction, have been identified primarily in the anterodorsal nucleus but only a few in the anteroventral nucleus and none in the anteromedial nucleus (Taube, 1998). It has been assumed that HD cells and also place cells (cells that preferentially discharge depending on the animals' location; these place cells have been identified in the hippocampus; O'Keefe & Nadel, 1978) provide the animal with a continuous indication of its orientation in space and enable it to navigate through its environment. Recent evidence of recordings of HD cells in the anterodorsal nucleus (AD) during spatial tests indicates that rats do not rely on these HD cells at least to make accurate responses in the spatial tasks, despite the HD cells role in maintaining a sense of direction (Golob et al, 2001). Furthermore lesions to the sub-nuclei of the AT have implicated each of them in spatial memory (Aggleton et al, 1996; Byatt & Dalrymple-Alford, 1996; van Groen & Wyss, 2002) but only the AD has a significant number of HD cells. The evidence thus far regarding the HD cells is very interesting and is clearly related to navigation of the animal in space but it does not appear sufficient to be able to propose that the deficits in spatial memory processing are the result of damage to the HD cells in the AT.

Furthermore, head direction cells have also been identified in other structures of the brain, for example in the laterodorsal thalamic (LD) nucleus (Muller, Ranck & Taube,

1996). It has been shown that the LD nucleus is prominently connected to the cortical structures (e.g. the superior colliculus) and primary and secondary visual cortical regions (Van Groen & Wyss, 1992) and is likely to be involved in relaying visual information to the limbic system (Mizumori et al, 1994; Golob et al, 1998; Van Groen & Wyss, 1992, 2003). Interestingly, dysfunction in the LD also causes some spatial memory impairment (Mizumori et al, 1993; Van Groen et al, 2002; Warburton, et al 1997). As previously noted, the current lesions to the AT produced very little atrophy in the laterodorsal thalamic nuclei (see Tables 9, 11, 13) thus it may be concluded that the AT and LD, both contribute to spatial memory processing in animals but in the case of the current behavioural evidence at least, the AT in itself is sufficient to produce deficits in spatial memory.

10.5 Further Conclusions Generated from the Empirical Findings

The correlational relationships between the amount of damage sustained in the target aggregates and memory impairments on the various behavioural tasks were very compelling. Firstly, it appears that lesions that damage the total extent of the individual target nuclei are not necessary for rats to be severely impaired on either of the spatial memory tasks, the memory for reward value task or the working memory for egocentric response assessed in the current research. Instead, the correlations implied that damage sustained to around 50% and above of the target structures was sufficient (although even less was sufficient for the AT deficits to occur on spatial memory). This conclusion in relation to the spatial memory tasks at least has been suggested by previous researchers, who reported deficits in spatial memory following subtotal lesions to the anteroventral and / or the anteromedial thalamic nuclei (Aggleton et al, 1996; Byatt and Dalrymple-Alford, 1996; van Groen & Wyss, 2002) and following microinfusions of scopolamine (a muscarinic antagonist) directly into the AT aimed at the highest density of cholinergic cells in the anteroventral nucleus especially (Mitchell et al, 2002). Moreover the evidence that less than 50% damage is required to cause memory impairments may also suggest why other researchers with larger lesions targeted at the MDn and ILn have deficits in spatial memory when lesions encroach into the AT but do not destroy the AT nuclei completely

(Burk & Mair, 1998; Hunt & Aggleton, 1991, 1998; Mair et al, 1998; Savage et al, 1998; Young et al, 1996).

In addition, related evidence for amnesic deficits following only partial damage to the AT nuclei has been reported in neuropathological reports of Korsakoff's syndrome patients (Harding et al, 2000). As discussed in Chapter 4, Harding and colleagues reported from their systematic investigations of KS patients, who have severe amnesia, that the critical cell loss needed for diencephalic amnesia occurred in the AT, with a reduction from 15% cell loss in non-amnesic alcoholics and Wernicke's patients to 50% cell loss in the AT.

The second related finding that was evident from the behavioural assessments showed that more extensive damage that was sustained across two or three of the medial thalamus targets caused additive memory impairments. These additive effects of memory impairment can be made more clearly by use of the example related to the spatial memory tasks, although only AT lesions were shown to cause impairments in spatial memory, lesions that caused similar damage to the AT but also substantial damage to the LT and MT thalamic aggregates were substantially more impaired at spatial memory processing. Our evidence is in accord with other evidence from the animal literature, which has also reported greater effects on memory impairments with AT lesions that have also encroached into other medial thalamic nuclei (Aggleton et al, 1996; Warburton et al, 1997, 1999). For example, comparative assessments of AT damage with combined AT and LD damage or fornix damage in rats were made during tests of spatial memory. It was reported that all lesion groups showed severe and long-lasting impairments compared with control rats, however the combined AT–LD lesion group was significantly worse than the fornix lesion group on a T-maze spatial alternation task (Warburton et al, 1997).

These additive effects of medial thalamic damage are also important for our understanding of thalamic amnesia in human clinical cases. As reported in the human literature, damage sustained in the medial thalamus is not specific to one particular grouping of thalamic nuclei. Therefore the deficits produced from even relatively small infarcts or occlusions in vascular supply when sustained over several groupings of nuclei may cause variability in deficits, both in extent and magnitude for different individual cases. Recently, Van der Werf et al (2003) suggested that executive memory deficits were

more likely to result from combined lesions to the medial thalamic aggregates rather than from more selective damage to only one nucleus of the medial thalamus.

Theoretically speaking, the additive effects of larger lesions in the medial thalamus may be explained by the proposal that interactions exist between the parallel multiple memory systems, whereby they work both cooperatively and in competition with the information processing that they carry out. It is proposed that the prefrontal cortex regulates behavioural outputs by processing the information it receives from different pathways carrying different sources of information, which are competing for expression of behaviour with the 'winners' being those pathways with the strongest sources of support (Miller & Cohen, 2001). In relation to parallel multiple memory system theory, this notion of cooperative and competitive strategies has been observed between the basal ganglia and the hippocampus during learning, when it has been reported that both systems appear to be activated simultaneously and in parallel (McDonald & White, 1994; Packard & McGaugh, 1996). Then with extended training in a stimulus-response task, expressions of response-learning tendencies begin to overshadow previously dominant place learning strategies (Packard & McGaugh, 1996). This observation in strategies adopted for learning in which both memory systems can provide an adequate solution indicates that the hippocampal based memory system provides a more rapid form of learning that initially controls behaviour but eventually concedes to the slower form of learning associated with the stimulus-response associations (Mizumori and Leutgeb, 2001; Packard & Knowlton, 2002).

Furthermore in thalamic lesions models, researchers have suggested the cooperative and competitive effects of lesions causing damage to the medial thalamus. For example, some researchers have indicated that when damage in the MDn or ILn has affected spatial memory tasks that are sensitive to hippocampal dysfunction that prefrontal type deficits occur when solving the spatial tasks (Alexinsky, 2001; Burk & Mair, 1998; Hunt & Aggleton, 1998). Prefrontal cortex deficits can often be characterized as reflecting a tendency to perseverate with inefficient strategies or cause delay-independent deficits (Dias & Aggleton, 2000; Chudasama & Muir, 1997; Kesner, 2000; Ragozzino et al, 1999). The damage sustained in the MDn and ILn for these rats often has substantial overlap with the AT nucleus too though. Therefore it could be concluded that these MDn and ILn lesion rats are impaired across both prefrontal-like strategies and spatial-type strategies, thus

compounding the deficits of spatial memory. Thus when the lesions are more restricted as is the case with the lesions in the current research, these prefrontal cortex like symptoms are not observed as other functional systems are able to compensate for the subsequent disruptions in the interdependent neural circuits.

Interestingly across the studies in the current research, there was some speculative evidence of similar behavioural performance for the LT aggregate. For example, in the egocentric response task, the lesion to the LT aggregate produced significant deficits in the memory for egocentric response compared to pre-surgery levels. However the current memory impairments were somewhat different to previous chance performance levels on the same task following lesion to the dorsomedial PFC (Ragozzino & Kesner, 2001). Perhaps the ability of the rats to perform above chance in the current research could suggest a higher level of motivation despite the impairments, for if performance is only at or below chance this could indicate a lack of motivation to perform accurately. Furthermore, LT lesion rats showed fewer premature responses (dark errors) during the sustained attention task than both controls and MD rats, which could also indicate a heightened level of motivation or attention to perform. However, the current proposals can only be speculative about the disruptions of the LT on functioning in the prefrontal cortex until further investigation using other techniques is conducted.

10.6 Unresolved Issues of the Current Research and Future Directions

It is important to note that the neuroanatomical re-assessment of the current research should be considered fluid, that is to say that the re-assessment relied upon the thorough investigations of other researchers tracing studies with current techniques available but in the future additional thalamic nuclei may be linked to these three independent aggregates or new aggregates may be identified with the development of further more advanced tracing and immunohistochemistry techniques.

One discrepancy in the behavioural assessments of this research related to the medial thalamus and the deficits in temporal order processing. It is proposed that the hippocampus (Kesner, 1998) and prefrontal cortex (Kesner, 2000) play a role in temporal aspects of information processing. However evidence from the current behavioural assessments did

not implicate the AT aggregate, which is prominently connected with the hippocampal system, in temporal order memory, but rather the MT and LT aggregates (Chapter 7). Aspects of temporal memory are affected following brain injury in the medial thalamus. Clinical evidence from Korsakoff syndrome patients and those suffering infarcts shows difficulties with temporal sequencing of episodic and biographical events, superimposition of temporally unrelated information and list discriminations (Downes et al, 2002; Ghika-Schmid & Bogousslavsky, 2000; Kopelman, 2000; Schmahmann, 2003). Therefore further investigations are necessary, especially in relation to a temporal order memory task that will show consistent capabilities of the control rats (see Chapter 9). It is also important to qualify the tests of temporal order memory, for example the task used in the current behavioural assessments assessed relative familiarity over novelty of two familiar objects presented at different times, while some other tasks assessing temporal order memory assess differences in item list discriminations or the relative recency of familiar repetitious stimuli, which is impaired following fornix damage in monkeys (Buckley et al, 2004). Further investigations are also warranted into other specific attributes of memory in which the independent medial thalamic aggregates may play a role. These investigations must incorporate a range of assessments including behaviour, and brain cell-mapping immunohistochemistry techniques. Brain cell-mapping techniques used to investigate connected structures of the extended hippocampal system using the immediate early gene, fos, have thus far been successful in mapping activated structures throughout the brain that are engaged during testing of spatial memory (Vann et al, 2000a, b). Investigations of activated brain structures following assessments of other attributes of memory, for example, affect, response, and temporal processes are necessary. Although it must be noted that the brain cell-mapping techniques incorporating immediate early gene activation implies a common relationship in the tasks performed before perfusion, however, caution must remain as other unrelated experiences may also trigger the gene proteins to become active (Aggleton & Pearce, 2001).

The MT aggregate was not included in the egocentric response memory task because previous evidence has suggested that the amygdala based memory system (of which the MT aggregate is proposed to be a part of) is not involved in response or stimulus-response learning (Kesner et al, 1993; McDonald & Hong, 2004; McDonald & White, 1993) or

spatial working memory (cf. Chapter 7; Aggleton & Brown, 1999; Kesner, 1998; McDonald & White, 2002). Nevertheless it would be necessary in future experiments to determine whether the specific components of the MT aggregate identified in the current research as the medial and central segments of the mediodorsal nucleus and intermediodorsal nucleus contribute a role to egocentric / response-based memory.

10.7 Summary

In summary then, the amnesic syndrome associated with thalamic amnesia does not appear to be caused by damage to just one medial thalamic grouping of nuclei. As explained in this thesis, this does not seem plausible for several reasons. Firstly the variability of cognitive and behavioural deficits and their magnitude in expression associated with thalamic amnesia is too broad for one thalamic grouping to be solely responsible. Secondly, damage is not sustained in just one medial thalamic nucleus in clinical cases; therefore it is not a case of simply dividing up the deficits to locate a common denominator amongst them. Thirdly, it is not necessary for total damage to be sustained in medial thalamic nuclei for memory deficits to occur. Fourth, in light of the current behavioural evidence the damage sustained to the medial thalamus and fibre pathways reported in clinical cases has been re-positioned within multiple memory systems each responsible for different attributes of memory. Therefore the damage sustained in the thalamic amnesic cases reflects the variability in lesion damage across a range of independent memory systems involved in both cooperative and competitive ways to influence behavioural outputs. Furthermore, by incorporating this type of understanding into clinical applications, the final outcome will involve greater understanding of the amnesic deficits for both the clinicians and their patients and families. Finally this current behavioural evidence supports the notion that neural circuits throughout the whole brain support learning and memory processes, amongst their other functionally related activities. Therefore this current research challenges some of the traditional views proposed about memory and contributes to a revision of diencephalic amnesia.

References

Adams KM, Gilman S, Koeppe RA, Kluin KJ, Brunberg JA, Dede D, Berent S, Kroll PD (1993) Neuropsychological deficits are correlated with frontal hypometabolism in positron emission tomography studies of older alcoholic patients. Alcohol Clin Exp Res 17:205-10.

Adolphs R, Tranel D (2003) Amygdala damage impairs emotion recognition from scenes only when they contain facial expressions. Neuropsychologia 41:1281-1289.

Adolphs R, Tranel D (2004) Impaired judgments of sadness but not happiness following bilateral amygdala damage. J Cogn Neurosci 16:453-462.

Adolphs R, Tranel D, Denburg N (2000) Impaired emotional declarative memory following unilateral amygdala damage. Learn Mem 7:180-186.

Aggleton JP (1986) Memory impairments caused by experimental thalamic lesions in monkeys. Rev Neurol (Paris) 142:418-424.

Aggleton JP (1993) The contribution of the amygdala to normal and abnormal emotional states. Trends Neurosci 16:328-333.

Aggleton JP, Brown MW (1999) Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. Behav Brain Sci 22:425-444; discussion 444-489.

Aggleton JP, Desimone R, Mishkin M (1986) The origin, course, and termination of the hippocampothalamic projections in the macaque. J Comp Neurol 243:409-421.

Aggleton JP, Hunt PR, Nagle S, Neave N (1996) The effects of selective lesions within the anterior thalamic nuclei on spatial memory in the rat. Behav Brain Res 81:189-198.

Aggleton JP, Keith AB, Sahgal A (1991) Both fornix and anterior thalamic, but not mammillary, lesions disrupt delayed non-matching-to-position memory in rats. Behav Brain Res 44:151-161.

Aggleton JP, McMackin D, Carpenter K, Hornak J, Kapur N, Halpin S, Wiles CM, Kamel H, Brennan P, Carton S, Gaffan D (2000) Differential cognitive effects of colloid cysts in the third ventricle that spare or compromise the fornix. Brain 123:800-815.

Aggleton JP, Mishkin M (1983) Visual recognition impairment following medial thalamic lesions in monkeys. Neuropsychologia 21:189-97.

Aggleton JP, Mishkin M (1983) Memory impairments following restricted medial thalamic lesions in monkeys. Exp Brain Res 52:199-209.

Aggleton JP, Neave N, Nagle S, Sahgal A (1995a) A comparison of the effects of medial prefrontal, cingulate cortex, and cingulum bundle lesions on tests of spatial memory: evidence of a double dissociation between frontal and cingulum bundle contributions. J Neurosci 15:7270-7281.

Aggleton JP, Neave N, Nagle S, Hunt PR (1995b) A comparison of the effects of anterior thalamic, mamillary body and fornix lesions on reinforced spatial alternation. Behav Brain Res 68:91-101.

Aggleton JP, Pearce JM (2001) Neural systems underlying episodic memory: insights from animal research. Philos Trans R Soc Lond B Biol Sci 356:1467-1482.

Aggleton JP, Sahgal A (1993) The contribution of the anterior thalamic nuclei to anterograde amnesia. Neuropsychologia 31:1001-1019.

Aggleton JP, Shaw C (1996) Amnesia and recognition memory: a re-analysis of psychometric data. Neuropsychologia 34:51-62.

Aggleton JP, Saunders RC (1997) The relationships between temporal lobe and diencephalic structures implicated in anterograde amnesia. Memory 5:49-71.

Alexander GE, Crutcher MD, DeLong MR (1990) Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res 85:119-46.

Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9:357-81.

Alexinsky T (2001) Differential effect of thalamic and cortical lesions on memory systems in the rat. Behav Brain Res 122:175-191.

Amaral DG, Witter, M. P., ed (1995) Hippocampal Formation, 2nd Edition. Sydney: Academic Press, Inc.

Asanuma (1997) In: Thalamus Vol 2: Experimental and Clinical Aspects. (Steriade M, Jones EJ, eds). Amsterdam: Elsevier.

Baddeley A (2001) The concept of episodic memory. Philos Trans R Soc Lond B Biol Sci 356:1345-1350.

Baddeley A (2003a) Double dissociations: not magic, but still useful. Cortex 39:129-131.

Baddeley A (2003b) Working memory: looking back and looking forward. Nat Rev Neurosci 4:829-839.

Baddeley AD, Warrington EK (1973) Memory coding and amnesia. Neuropsychologia 11:159-165.

Belzunegui T, Insausti R, Ibanez J, Gonzalo LM (1995) Effect of chronic alcoholism on neuronal nuclear size and neuronal population in the mammillary body and the anterior thalamic complex of man. Histol Histopathol 10:633-638.

Benke T, Kurzthaler I, Schmidauer C, Moncayo R, Donnemiller E (2002) Mania caused by a diencephalic lesion. Neuropsychologia 40:245-252.

Bentivoglio M, Kultas-Ilinsky K, Ilinsky I (1993) Limbic Thalamus: Structure, Intrinsic Organization, and Connections. In: Neurobiology of Cingulate Cortex and Limbic Thalamus: A comprehensive handbook (Vogt BA, Gabriel M, eds). Boston: Birkhauser.

Beracochea D, Jaffard R (1991) Effects of chronic ethanol consumption associated or not with experimental anterior thalamic lesions on spontaneous sequential alternation in mice. Neurosci Lett 134:45-48.

Beracochea DJ, Jaffard R, Jarrard LE (1989) Effects of anterior or dorsomedial thalamic ibotenic lesions on learning and memory in rats. Behav Neural Biol 51:364-376.

Berendse HW, Groenewegen HJ (1990) Organization of the thalamostriatal projections in the rat, with special emphasis on the ventral striatum. J Comp Neurol 299:187-228.

Berendse HW, Groenewegen HJ (1991) Restricted cortical termination fields of the midline and intralaminar thalamic nuclei in the rat. Neuroscience 42:73-102.

Birrell JM, Brown VJ (2000) Medial frontal cortex mediates perceptual attentional set shifting in the rat. J Neurosci 20:4320-4.

Blaha CD, Allen LF, Das S, Inglis WL, Latimer MP, Vincent SR, Winn P (1996) Modulation of dopamine efflux in the nucleus accumbens after cholinergic stimulation of the ventral tegmental area in intact, pedunculopontine tegmental nucleus-lesioned, and laterodorsal tegmental nucleus-lesioned rats. J Neurosci 16:714-722.

Bland BH, Konopacki J, Kirk IJ, Oddie SD, Dickson CT (1995) Discharge patterns of hippocampal theta-related cells in the caudal diencephalon of the urethan-anesthetized rat. J Neurophysiol 74:322-33.

Bogousslavsky J, Regli F, Uske A (1988) Thalamic infarcts: clinical syndromes, etiology, and prognosis. Neurology 38:837-848.

Bold EL, Castro AJ, Neafsey EJ (1984) Cytoarchitecture of the dorsal thalamus of the rat. Brain Res Bull 12:521-527.

Braak H, Braak E, Yilmazer D, de Vos RA, Jansen EN, Bohl J (1996) Pattern of brain destruction in Parkinson's and Alzheimer's diseases. J Neural Transm 103:455-90.

Braak H, Braak E (1991) Alzheimer's disease affects limbic nuclei of the thalamus. Acta Neuropathol (Berl) 81:261-8.

Brand M, Fujiwara E, Kalbe E, Steingass HP, Kessler J, Markowitsch HJ (2003) Cognitive estimation and affective judgments in alcoholic Korsakoff patients. J Clin Exp Neuropsychol 25:324-334.

Broadbent NJ, et al (2002) In Neuropsychology of Memory. 3rd ed. LR Squire & DL Schacter Eds. New York: Guildford Press

Broersen LM, Uylings HB (1999) Visual attention task performance in Wistar and Lister hooded rats: response inhibition deficits after medial prefrontal cortex lesions. Neuroscience 94:47-57.

Broersen LM (2000) Attentional processes and learning and memory in rats: the prefrontal cortex and hippocampus compared. Prog Brain Res 126:79-94.

Brown MW, Aggleton JP (2001) Recognition memory: what are the roles of the perirhinal cortex and hippocampus? Nat Rev Neurosci 2:51-61.

Buckley MJ, Charles DP, Browning PG, Gaffan D (2004) Learning and retrieval of concurrently presented spatial discrimination tasks: role of the fornix. Behav Neurosci 118:138-49.

Burk JA, Mair RG (1998) Thalamic amnesia reconsidered: excitotoxic lesions of the intralaminar nuclei, but not the mediodorsal nucleus, disrupt place delayed matching-to-sample performance in rats (Rattus norvegicus). Behav Neurosci. 112:54-67

Burk JA, Mair RG (2001a) Effects of intralaminar thalamic lesions on sensory attention and motor intention in the rat: a comparison with lesions involving frontal cortex and hippocampus. Behav Brain Res 123:49-63.

Burk JA, Mair RG (2001b) Effects of dorsal and ventral striatal lesions on delayed matching trained with retractable levers. Behav Brain Res 122:67-78.

Burwell RD, Witter MP, Amaral DG (1995) Perirhinal and postrhinal cortices of the rat: a review of the neuroanatomical literature and comparison with findings from the monkey brain. Hippocampus 5:390-408.

Bussey TJ, Muir JL, Everitt BJ, Robbins TW (1997) Triple dissociation of anterior cingulate, posterior cingulate, and medial frontal cortices on visual discrimination tasks using a touchscreen testing procedure for the rat. Behav Neurosci 111:920-36.

Byatt G, Dalrymple-Alford JC (1996) Both anteromedial and anteroventral thalamic lesions impair radial-maze learning in rats. Behav Neurosci 110:1335-1348.

Calabrese P, Haupts M, Markowitsch HJ, Gehlen W (1993) The cognitive-mnestic performance profile of a patient with bilateral asymmetrical thalamic infarction. Int J Neurosci. 71:101-6

Cahill L, Babinsky R, Markowitsch HJ, McGaugh JL (1995) The amygdala and emotional memory. Nature 377:295-296.

Celerier A, Ognard R, Decorte L, Beracochea D (2000) Deficits of spatial and non-spatial memory and of auditory fear conditioning following anterior thalamic lesions in mice: comparison with chronic alcohol consumption. Eur J Neurosci 12:2575-2584.

Cheatwood JL, Reep RL, Corwin JV (2003) The associative striatum: cortical and thalamic projections to the dorsocentral striatum in rats. Brain Res 968:1-14.

Chudasama Y, Muir JL (1997) A behavioural analysis of the delayed non-matching to position task: the effects of scopolamine, lesions of the fornix and of the prelimbic region on mediating behaviours by rats. Psychopharmacology (Berl) 134:73-82.

Chudasama Y, Muir JL (2001) Visual attention in the rat: a role for the prelimbic cortex and thalamic nuclei? Behav Neurosci 115:417-428.

Chudasama Y, Bussey TJ, Muir JL (2001) Effects of selective thalamic and prelimbic cortex lesions on two types of visual discrimination and reversal learning. Eur J Neurosci 14:1009-1020.

Cohen NJ, Eichenbaum H (1993) Memory, amnesia, and the hippocampal system. Cambridge: MIT Press

Cohen NJ, Squire LR (1980) Preserved learning and retention of pattern-analyzing skill in amnesia: dissociation of knowing how and knowing that. Science 210:207-210.

Collins SJ, Lawson VA, Masters CL (2004) Transmissible spongiform encephalopathies. Lancet 363:51-61.

Conde F, Audinat E, Maire-Lepoivre E, Crepel F (1990) Afferent connections of the medial frontal cortex of the rat. A study using retrograde transport of fluorescent dyes. I. Thalamic afferents. Brain Res Bull 24:341-54.

Conde F, Maire-Lepoivre E, Audinat E, Crepel F (1995) Afferent connections of the medial frontal cortex of the rat. II. Cortical and subcortical afferents. J Comp Neurol 352(4):567-93.

Cook D, Kesner RP (1988) Caudate nucleus and memory for egocentric localization. Behav Neural Biol 49:332-343.

Corbetta M, Miezin FM, Dobmeyer S, Shulman GL, Petersen SE (1991) Selective and divided attention during visual discriminations of shape, color, and speed: functional anatomy by positron emission tomography. J Neurosci 11:2383-402.

Corbit LH, Muir JL, Balleine BW (2003) Lesions of mediodorsal thalamus and anterior thalamic nuclei produce dissociable effects on instrumental conditioning in rats. Eur J Neurosci 18:1286-1294.

Corkin S (2002) What's new with the amnesic patient H.M.? Nat Rev Neurosci 3:153-160.

Corkin S, Amaral DG, Gonzalez RG, Johnson KA, Hyman BT (1997) H. M.'s medial temporal lobe lesion: findings from magnetic resonance imaging. J Neurosci 17:3964-3979.

Cornwall J, Cooper JD, Phillipson OT (1990) Afferent and efferent connections of the laterodorsal tegmental nucleus in the rat. Brain Res Bull. 25:271-84

Courtiere A, Hardouin J (1997) Behavioural effects induced by nitrous oxide in rats performing a vigilance task. Behav Pharmacol 8:408-15.

Daum I, Ackermann H (1994a) Frontal-type memory impairment associated with thalamic damage. Int J Neurosci 77:187-198.

Daum I, Ackermann H (1994b) Dissociation of declarative and nondeclarative memory after bilateral thalamic lesions: a case report. Int J Neurosci 75:153-165.

Daum I, Graber S, Schugens MM, Mayes AR (1996) Memory dysfunction of the frontal type in normal ageing. Neuroreport 7:2625-8.

DeCoteau WE, Kesner RP (1998) Effects of hippocampal and parietal cortex lesions on the processing of multiple-object scenes. Behav Neurosci 112:68-82.

DeCoteau WE, Kesner RP, Williams JM (1997) Short-term memory for food reward magnitude: the role of the prefrontal cortex. Behav Brain Res 88:239-249.

Delatour B, Gisquet-Verrier P (2001) Involvement of the dorsal anterior cingulate cortex in temporal behavioral sequencing: subregional analysis of the medial prefrontal cortex in rat. Behav Brain Res 126:105-114.

Delatour B, Gisquet-Verrier P (1999) Lesions of the prelimbic-infralimbic cortices in rats do not disrupt response selection processes but induce delay-dependent deficits: evidence for a role in working memory? Behav Neurosci 113:941-55.

Delatour B, Gisquet-Verrier P (1996) Prelimbic cortex specific lesions disrupt delayed-variable response tasks in the rat. Behav Neurosci 110:1282-98.

Devan BD, McDonald RJ, White NM (1999) Effects of medial and lateral caudate-putamen lesions on place- and cue-guided behaviors in the water maze: relation to thigmotaxis. Behav Brain Res 100:5-14.

Devan BD, White NM (1999) Parallel information processing in the dorsal striatum: relation to hippocampal function. J Neurosci 19:2789-2798.

Dias R, Aggleton JP (2000) Effects of selective excitotoxic prefrontal lesions on acquisition of nonmatching- and matching-to-place in the T-maze in the rat: differential involvement of the prelimbic-infralimbic and anterior cingulate cortices in providing behavioural flexibility. Eur J Neurosci 12:4457-4466.

Diederich N, Goetz CG, Stebbins GT, Klawans HL, Nittner K, Koulosakis A, Sanker P, Sturm V (1992) Blinded evaluation confirms long-term asymmetric effect of unilateral thalamotomy or subthalamotomy on tremor in Parkinson's disease. Neurology 42:1311-4.

Dix SL, Aggleton JP (1999) Extending the spontaneous preference test of recognition: evidence of object-location and object-context recognition. Behav Brain Res 99:191-200.

Downes JJ, Mayes AR, MacDonald C, Hunkin NM (2002) Temporal order memory in patients with Korsakoff's syndrome and medial temporal amnesia. Neuropsychologia. 40:853-61

Dusoir H, Kapur N, Byrnes DP, McKinstry S, Hoare RD (1990) The role of diencephalic pathology in human memory disorder. Evidence from a penetrating paranasal brain injury. Brain 113 (Pt 6):1695-1706.

Easton A, Gaffan D (2000) Amygdala and the memory of reward: the importance of fibres of passage from the basal forebrain. In: The Amygdala, 2nd Ed Edition (Aggleton JP, ed). New York: Oxford University Press.

Easton A, Parker A (2003) A cholinergic explanation of dense amnesia. Cortex 39:813-826.

Edelstyn NM, Ellis SJ, Jenkinson P, Sawyer A (2002) Contribution of the left dorsomedial thalamus to recognition memory: a neuropsychological case study. Neurocase 8:442-452.

Eichenbaum H (1994) In: Memory Systems. DL Schacter & E Tulving Eds. MIT Press

Eichenbaum H (1999a) The hippocampus and mechanisms of declarative memory. Behav Brain Res 103:123-133.

Eichenbaum H (1999b) Neurobiology. The topography of memory. Nature 402:597-599.

Eichenbaum H, Cohen NJ (2001) From Conditioning to Conscious Recollection. New York: Oxford University Press.

Erro ME, Lanciego JL, Arribas J, Gimenez-Amaya JM (2001) Striatal input from the ventrobasal complex of the rat thalamus. Histochem Cell Biol 115:447-54.

Exner C, Weniger G, Irle E (2001) Implicit and explicit memory after focal thalamic lesions. Neurology 57:2054-2063.

Fellows BJ (1967) Chance stimulus sequences for discrimination tasks. Psychol Bull 67:87-92.

Floresco SB, Braaksma DN, Phillips AG (1999a) Thalamic-cortical-striatal circuitry subserves working memory during delayed responding on a radial arm maze. J Neurosci 19:11061-11071.

Floresco SB, Braaksma DN, Phillips AG (1999b) Involvement of the ventral pallidum in working memory tasks with or without a delay. Ann N Y Acad Sci 877:711-716.

Freeman JH, Jr., Cuppernell C, Flannery K, Gabriel M (1996a) Limbic thalamic, cingulate cortical and hippocampal neuronal correlates of discriminative approach learning in rabbits. Behav Brain Res 80:123-136.

Freeman JH, Jr., Cuppernell C, Flannery K, Gabriel M (1996b) Context-specific multi-site cingulate cortical, limbic thalamic, and hippocampal neuronal activity during concurrent discriminative approach and avoidance training in rabbits. J Neurosci 16:1538-1549.

Fuster JM (2001) The prefrontal cortex--an update: time is of the essence. Neuron 30:319-333.

Gabriel M (1993) Discriminative Avoidance Learning: A Model System. In: Neurobiology of Cingulate Cortex and Limbic Thalamus: A comprehensive handbook (Vogt BA, Gabriel M, eds). Boston: Birkhauser.

Gaffan D (1992) Amnesia for Complex Naturalistic Scenes and for Objects Following Fornix Transection in the Rhesus Monkey. Eur J Neurosci 4:381-388.

Gaffan D (1994) Role of the amygdala in picture discrimination learning with 24-h intertrial intervals. Exp Brain Res 99:423-430.

Gaffan D (2002) Against memory systems. Philos Trans R Soc Lond B Biol Sci 357:1111-1121.

Gaffan D, Easton A, Parker A (2002) Interaction of inferior temporal cortex with frontal cortex and basal forebrain: double dissociation in strategy implementation and associative learning. J Neurosci 22:7288-7296.

Gaffan D, Murray EA (1990) Amygdalar interaction with the mediodorsal nucleus of the thalamus and the ventromedial prefrontal cortex in stimulus-reward associative learning in the monkey. J Neurosci 10:3479-3493.

Gaffan D, Murray EA, Fabre-Thorpe M (1993) Interaction of the amygdala with the frontal lobe in reward memory. Eur J Neurosci 5:968-75.

Gaffan D, Parker A (2000) Mediodorsal thalamic function in scene memory in rhesus monkeys. Brain 123:816-827.

Gaffan D, Parker A, Easton A (2001a) Dense amnesia in the monkey after transection of fornix, amygdala and anterior temporal stem. Neuropsychologia 39:51-70.

Gaffan EA, Aggleton JP, Gaffan D, Shaw C (1990) Concurrent and sequential pattern discrimination learning by patients with Korsakoff amnesia. Cortex 26:381-397.

Gaffan EA, Bannerman DM, Warburton EC, Aggleton JP (2001b) Rats' processing of visual scenes: effects of lesions to fornix, anterior thalamus, mamillary nuclei or the retrohippocampal region. Behav Brain Res 121:103-117.

George MS, Anton RF, Bloomer C, Teneback C, Drobes DJ, Lorberbaum JP, Nahas Z, Vincent DJ (2001) Activation of prefrontal cortex and anterior thalamus in alcoholic subjects on exposure to alcohol-specific cues. Arch Gen Psychiatry 58:345-352.

Gerfen CR (1992) The neostriatal mosaic: multiple levels of compartmental organization. Trends Neurosci 15:133-9.

Ghika-Schmid F, Bogousslavsky J (2000) The acute behavioral syndrome of anterior thalamic infarction: a prospective study of 12 cases. Ann Neurol 48:220-227.

Gilbert PE, Campbell A, Kesner RP (2003) The role of the amygdala in conditioned flavor preference. Neurobiol Learn Mem 79:118-121.

Gilbert PE, Kesner RP (2002) The amygdala but not the hippocampus is involved in pattern separation based on reward value. Neurobiol Learn Mem 77:338-353.

Gilbert PE, Kesner RP, DeCoteau WE (1998) Memory for spatial location: role of the hippocampus in mediating spatial pattern separation. J Neurosci 18:804-810.

Gilbert PE, Kesner RP, Lee I (2001) Dissociating hippocampal subregions: double dissociation between dentate gyrus and CA1. Hippocampus 11:626-636.

Goldman-Rakic PS (1995) Architecture of the prefrontal cortex and the central executive. Ann N Y Acad Sci 769:71-83.

Golob EJ, Stackman RW, Wong AC, Taube JS (2001) On the behavioral significance of head direction cells: neural and behavioral dynamics during spatial memory tasks. Behav Neurosci 115:285-304.

Golob EJ, Wolk DA, Taube JS (1998) Recordings of postsubiculum head direction cells following lesions of the laterodorsal thalamic nucleus. Brain Res 780:9-19.

Graff-Radford NR, Tranel D, Van Hoesen GW, Brandt JP (1990) Diencephalic amnesia. Brain 113:1-25.

Granon S, Hardouin J, Courtier A, Poucet B (1998) Evidence for the involvement of the rat prefrontal cortex in sustained attention. Q J Exp Psychol B 51:219-33.

Groenewegen HJ (1988) Organization of the afferent connections of the mediodorsal thalamic nucleus in the rat, related to the mediodorsal-prefrontal topography. Neuroscience 24:379-431.

Groenewegen HJ, Berendse HW (1994) The specificity of the 'nonspecific' midline and intralaminar thalamic nuclei. Trends Neurosci 17:52-57.

Groenewegen HJ, Berendse HW, Haber SN (1993) Organization of the output of the ventral striatopallidal system in the rat: ventral pallidal efferents. Neuroscience 57:113-142.

Groenewegen HJ, Berendse HW, Wolters JG, Lohman AH (1990) The anatomical relationship of the prefrontal cortex with the striatopallidal system, the thalamus and the amygdala: evidence for a parallel organization. Prog Brain Res 85:95-116; discussion 116-118.

Groenewegen HJ, Galis-de Graaf Y, Smeets WJ (1999a) Integration and segregation of limbic cortico-striatal loops at the thalamic level: an experimental tracing study in rats. J Chem Neuroanat 16:167-185.

Groenewegen HJ, Uylings HB (2000) The prefrontal cortex and the integration of sensory, limbic and autonomic information. Prog Brain Res 126:3-28.

Groenewegen HJ, Van Dijk CA (1984) Efferent connections of the dorsal tegmental region in the rat, studied by means of anterograde transport of the lectin Phaseolus vulgaris-leucoagglutinin (PHA-L). Brain Res 304:367-371.

Groenewegen HJ, Vermeulen-Van der Zee E, te Kortschot A, Witter MP (1987) Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of Phaseolus vulgaris leucoagglutinin. Neuroscience 23:103-120.

Groenewegen HJ, Wright CI, Beijer AV, Voorn P (1999b) Convergence and segregation of ventral striatal inputs and outputs. Ann N Y Acad Sci 877:49-63.

Groenewegen HJ, Wright CI, Uylings HB (1997) The anatomical relationships of the prefrontal cortex with limbic structures and the basal ganglia. J Psychopharmacol 11:99-106.

Grosse Beilage E, Robinson JK, Koger SM, Fox GD, Zhang YP (1992) Delayed-nonmatching-to-sample performance is impaired by extensive, but not by limited, lesions of the thalamus in the rat. Behav Neurosci 106:646-656.

Grossman M, Butters N (1986) The appreciation of affect in alcoholic Korsakoff patients. Int J Neurosci 30:1-9.

Haber SN, Wolfe DP, Groenewegen HJ (1990) The relationship between ventral striatal efferent fibers and the distribution of peptide-positive woolly fibers in the forebrain of the rhesus monkey. Neuroscience 39:323-38.

Hallanger AE, Levey AI, Lee HJ, Rye DB, Wainer BH (1987) The origins of cholinergic and other subcortical afferents to the thalamus in the rat. J Comp Neurol 262:105-24.

Hallanger AE, Price SD, Lee HJ, Steininger TL, Wainer BH (1990) Ultrastructure of cholinergic synaptic terminals in the thalamic anteroventral, ventroposterior, and dorsal lateral geniculate nuclei of the rat. J Comp Neurol 299:482-92.

Harding A, Halliday G, Caine D, Kril J (2000) Degeneration of anterior thalamic nuclei differentiates alcoholics with amnesia. Brain 123:141-154.

Harding AJ, Wong A, Svoboda M, Kril JJ, Halliday GM (1997) Chronic alcohol consumption does not cause hippocampal neuron loss in humans. Hippocampus 7:78-87.

Harper C, Dixon G, Sheedy D, Garrick T (2003) Neuropathological alterations in alcoholic brains. Studies arising from the New South Wales Tissue Resource Centre. Prog Neuropsychopharmacol Biol Psychiatry. 27:951-61

Harrison LM, Mair RG (1996) A comparison of the effects of frontal cortical and thalamic lesions on measures of spatial learning and memory in the rat. Behav Brain Res 75:195-206.

Hasselmo ME, Fransen E, Dickson C, Alonso AA (2000) Computational modeling of entorhinal cortex. Ann N Y Acad Sci 911:418-46.

Heimer L, Alheid GF, de Olmos JS, Groenewegen HJ, Haber SN, Harlan RE, Zahm DS (1997) The accumbens: beyond the core-shell dichotomy. J Neuropsychiatry Clin Neurosci 9:354-381.

Henderson JM, Carpenter K, Cartwright H, Halliday GM (2000a) Loss of thalamic intralaminar nuclei in progressive supranuclear palsy and Parkinson's disease: clinical and therapeutic implications. Brain 123 (Pt 7):1410-1421.

Henderson JM, Carpenter K, Cartwright H, Halliday GM (2000b) Degeneration of the centre median-parafascicular complex in Parkinson's disease. Ann Neurol 47:345-352.

Henderson JM, O'Sullivan DJ, Pell M, Fung VS, Hely MA, Morris JG, Halliday GM (2001) Lesion of thalamic centromedian--parafascicular complex after chronic deep brain stimulation. Neurology 56:1576-1579.

Holdstock JS, Mayes AR, Cezayirli E, Aggleton JP, Roberts N (1999) A comparison of egocentric and allocentric spatial memory in medial temporal lobe and Korsakoff amnesics. Cortex 35:479-501.

Holdstock JS, Mayes AR, Cezayirli E, Isaac CL, Aggleton JP, Roberts N (2000) A comparison of egocentric and allocentric spatial memory in a patient with selective hippocampal damage. Neuropsychologia 38:410-425.

Hunt PR, Aggleton JP (1991) Medial dorsal thalamic lesions and working memory in the rat. Behav Neural Biol 55:227-246.

Hunt PR, Aggleton JP (1998a) An examination of the spatial working memory deficit following neurotoxic medial dorsal thalamic lesions in rats. Behav Brain Res 97:129-141.

Hunt PR, Aggleton JP (1998b) Neurotoxic lesions of the dorsomedial thalamus impair the acquisition but not the performance of delayed matching to place by rats: a deficit in shifting response rules. J Neurosci 18:10045-10052.

Hunt PR, Neave N, Shaw C, Aggleton JP (1994) The effects of lesions to the fornix and dorsomedial thalamus on concurrent discrimination learning by rats. Behav Brain Res 62:195-205.

Inglis WL, Semba K (1997) Discriminable excitotoxic effects of ibotenic acid, AMPA, NMDA and quinolinic acid in the rat laterodorsal tegmental nucleus. Brain Res. 755(1):17-27

Jarrard LE (1993) On the role of the hippocampus in learning and memory in the rat. Behav Neural Biol 60:9-26.

Jenkins TA, Dias R, Amin E, Aggleton JP (2002a) Changes in Fos expression in the rat brain after unilateral lesions of the anterior thalamic nuclei. Eur J Neurosci 16:1425-1432.

Jenkins TA, Latimer MP, Alderson HL, Winn P (2002b) Determination of acetylcholine and dopamine content in thalamus and striatum after excitotoxic lesions of the pedunculopontine tegmental nucleus in rats. Neurosci Lett 322:45-48.

Jenkins TA, Dias R, Amin E, Brown MW, Aggleton JP (2002c) Fos imaging reveals that lesions of the anterior thalamic nuclei produce widespread limbic hypoactivity in rats. J Neurosci 22:5230-5238.

Johnson KA, Jones K, Holman BL, Becker JA, Spiers PA, Satlin A, Albert MS (1998) Preclinical prediction of Alzheimer's disease using SPECT. Neurology 50:1563-71.

Jones EG (1985). The Thalamus. Plenum Press.

Jones EG (1997). The Human Thalamus In: Thalamus Vol 2: Experimental and Clinical Aspects. (Steriade M, Jones EJ, eds). Amsterdam: Elsevier.

Kapur N, Abbott P, Lowman A, Will RG (2003) The neuropsychological profile associated with variant Creutzfeldt-Jakob disease. Brain 126:2693-2702.

Kapur N, Ironside J, Abbott P, Warner G, Turner A (2001) A neuropsychological-neuropathological case study of variant Creutzfeldt-Jakob disease. Neurocase 7:261-267.

Keating GL, Winn P (2002) Examination of the role of the pedunculopontine tegmental nucleus in radial maze tasks with or without a delay. Neuroscience. 112(3):687-96

Kesner RP (1998) Neurobiological Views of Memory. In: Neurobiology of Learning and Memory (Martinez JL, Kesner RP, eds). San Diego: Academic Press.

Kesner RP (2000) Subregional analysis of mnemonic functions of the prefrontal cortex in the rat. Psychobiology 28:219-228.

Kesner RP, Bolland BL, Dakis M (1993) Memory for spatial locations, motor responses, and objects: triple dissociation among the hippocampus, caudate nucleus, and extrastriate visual cortex. Exp Brain Res 93:462-470.

Kesner RP, Evans RB, Hunt MA (1987) Further evidence in support of the neurobiological bases of an attribute model of memory: role of the hippocampus. Int J Neurol 21-22:184-196.

Kesner RP, Farnsworth G, DiMattia BV (1989) Double dissociation of egocentric and allocentric space following medial prefrontal and parietal cortex lesions in the rat. Behav Neurosci 103:956-961.

Kesner RP, Gilbert PE, Barua LA (2002) The role of the hippocampus in memory for the temporal order of a sequence of odors. Behav Neurosci 116:286-290.

Kesner RP, Williams JM (1995) Memory for magnitude of reinforcement: dissociation between the amygdala and hippocampus. Neurobiol Learn Mem 64:237-244.

Kirk IJ, Oddie SD, Konopacki J, Bland BH (1996) Evidence for differential control of posterior hypothalamic, supramammillary, and medial mammillary theta-related cellular discharge by ascending and descending pathways. J Neurosci 16:5547-54.

Knowlton BJ, Squire LR (1995) Remembering and knowing: two different expressions of declarative memory. J Exp Psychol Learn Mem Cogn. 21:699-710.

Kocsis B, Di Prisco GV, Vertes RP. (2001) Theta synchronization in the limbic system: the role of Gudden's tegmental nuclei.Eur J Neurosci 13:381-8.

Kolb B, Pittman K, Sutherland RJ, Whishaw IQ (1982) Dissociation of the contributions of the prefrontal cortex and dorsomedial thalamic nucleus to spatially guided behavior in the rat. Behav Brain Res 6:365-378.

Kopelman MD (1995) The Korsakoff syndrome. Br J Psychiatry 166:154-173.

Kopelman MD (2002) Disorders of memory. Brain 125:2152-2190.

Kopelman MD, Stanhope N (1997) Rates of forgetting in organic amnesia following temporal lobe, diencephalic, or frontal lobe lesions. Neuropsychology 11:343-356.

Kopelman MD, Stanhope N, Kingsley D (1997) Temporal and spatial context memory in patients with focal frontal, temporal lobe, and diencephalic lesions. Neuropsychologia 35:1533-1545.

Kopelman MD, Stanhope N, Kingsley D (1999) Retrograde amnesia in patients with diencephalic, temporal lobe or frontal lesions. Neuropsychologia 37:939-958.

Kornecook TJ, Anzarut A, Pinel JP (1999) Rhinal cortex, but not medial thalamic, lesions cause retrograde amnesia for objects in rats. Neuroreport 10:2853-2858.

Krauss JK, Pohle T, Weigel R, Burgunder JM (2002) Deep brain stimulation of the centre median-parafascicular complex in patients with movement disorders. J Neurol Neurosurg Psychiatry 72:546-548.

Krazem A, Beracochea D, Jaffard R (1995) Effects of mammillary bodies and mediodorsal thalamic lesions on the acquisition and retention of a learning set in mice: paradoxical effect of the intersession interval. Behav Brain Res 67:51-58.

Krettek JE, Price JL (1977) The cortical projections of the mediodorsal nucleus and adjacent thalamic nuclei in the rat. J Comp Neurol 171:157-191.

Kril JJ, Halliday GM (1999) Brain shrinkage in alcoholics: a decade on and what have we learned? Prog Neurobiol 58:381-387.

Kril JJ, Halliday GM, Svoboda MD, Cartwright H (1997) The cerebral cortex is damaged in chronic alcoholics. Neuroscience 79:983-998.

Krout KE, Belzer RE, Loewy AD (2002) Brainstem projections to midline and intralaminar thalamic nuclei of the rat. J Comp Neurol 448:53-101.

Krout KE, Loewy AD (2000a) Parabrachial nucleus projections to midline and intralaminar thalamic nuclei of the rat. J Comp Neurol 428:475-494.

Krout KE, Loewy AD (2000b) Periaqueductal gray matter projections to midline and intralaminar thalamic nuclei of the rat. J Comp Neurol 424:111-141.

Krout KE, Loewy AD, Westby GW, Redgrave P (2001) Superior colliculus projections to midline and intralaminar thalamic nuclei of the rat. J Comp Neurol 431:198-216.

Langlais PJ, Mandel RJ, Mair RG (1992) Diencephalic lesions, learning impairments, and intact retrograde memory following acute thiamine deficiency in the rat. Behav Brain Res 48:177-185.

Langlais PJ, Savage LM (1995) Thiamine deficiency in rats produces cognitive and memory deficits on spatial tasks that correlate with tissue loss in diencephalon, cortex and white matter. Behav Brain Res 68:75-89.

Lee I, Kesner RP (2002) Differential contribution of NMDA receptors in hippocampal subregions to spatial working memory.Nat Neurosci. 5:162-8

Lee I, Kesner RP (2003) Time-dependent relationship between the dorsal hippocampus and the prefrontal cortex in spatial memory. J Neurosci. 23:1517-23.

Leutgeb S, Mizumori SJ (2002) Context-specific spatial representations by lateral septal cells. Neuroscience 112:655-663.

Levey AI, Hallanger AE, Wainer BH (1987) Choline acetyltransferase immunoreactivity in the rat thalamus. J Comp Neurol 257:317-32.

Lezak MD (1995) Neuropsychological Assessment 3rd ed. New York: Oxford University Press

Li L, Shao J (1998) Restricted lesions to ventral prefrontal subareas block reversal learning but not visual discrimination learning in rats. Physiol Behav 65:371-9.

Macchi (1997) In: Thalamus Vol 2: Experimental and Clinical Aspects. (Steriade M, Jones EJ, eds). Amsterdam: Elsevier.

Mair RG (1994) On the role of thalamic pathology in diencephalic amnesia. Rev Neurosci 5:105-140.

Mair RG, Burk JA, Porter MC (1998) Lesions of the frontal cortex, hippocampus, and intralaminar thalamic nuclei have distinct effects on remembering in rats. Behav Neurosci 112:772-792.

Mair RG, Burk JA, Porter MC (2003) Impairment of radial maze delayed nonmatching after lesions of anterior thalamus and parahippocampal cortex. Behav Neurosci 117:596-605.

Mair RG, Burk JA, Porter MC, Ley JE (1999) Thalamic amnesia and the hippocampus: Unresolved questions and an alternative candidate. Behav Brain Sci 22: 458-459.

Mair RG, Koch JK, Newman JB, Howard JR, Burk JA (2002) A double dissociation within striatum between serial reaction time and radial maze delayed nonmatching performance in rats. J Neurosci 22:6756-6765.

Mair RG, Lacourse DM (1992) Radio-frequency lesions of the thalamus produce delayed-nonmatching-to-sample impairments comparable to pyrithiamine-induced encephalopathy in rats. Behav Neurosci 106:634-645.

Mair RG, Otto TA, Knoth RL, Rabchenuk SA, Langlais PJ (1991) Analysis of aversively conditioned learning and memory in rats recovered from pyrithiamine-induced thiamine deficiency. Behav Neurosci 105:351-359.

Mair WG, Warrington EK, Weiskrantz L (1979) Memory disorder in Korsakoff's psychosis: a neuropathological and neuropsychological investigation of two cases. Brain 102:749-783.

Mandler G (1980) Recognising: The judgment of previous occurence. Psyc Rev 87:252-271.

Markowitsch HJ (1982) Thalamic mediodorsal nucleus and memory: a critical evaluation of studies in animals and man. Neurosci Biobehav Rev 6:351-380.

Markowitsch HJ (1988) Diencephalic amnesia: a reorientation towards tracts? Brain Res 472:351-370.

Markowitsch HJ (1998) Differential contribution of right and left amygdala to affective information processing. Behav Neurol 11:233-244.

Markowitsch HJ (1999) *Gestalt* view of the limbic system and the Papez circuit – another approach to unity and diversity of brain structures and functions. Behav Brain Sci 22: 459-460.

Markowitsch HJ, Calabrese P, Wurker M, Durwen HF, Kessler J, Babinsky R, Brechtelsbauer D, Heuser L, Gehlen W (1994) The amygdala's contribution to memory--a study on two patients with Urbach-Wiethe disease. Neuroreport 5:1349-52.

Markowitsch HJ, Vandekerckhovel MM, Lanfermann H, Russ MO (2003) Engagement of lateral and medial prefrontal areas in the ecphory of sad and happy autobiographical memories. Cortex 39:643-65.

Mayes AR, Meudell PR, Mann D, Pickering A (1988) Location of lesions in Korsakoff's syndrome: neuropsychological and neuropathological data on two patients. Cortex 24:367-388.

McDaniel WF, Via JD, Smith JS, Wells DL, Fu JJ, Bishop JF, Boyd PA, Ledesma HM (1995) Unilateral injury of posterior parietal cortex and spatial learning in hooded rats. Behav Brain Res 70:165-79.

McDonald AJ (1998) Cortical pathways to the mammalian amygdala. Prog Neurobiol 55:257-332.

McDonald RJ, White NM (1993) A triple dissociation of memory systems: hippocampus, amygdala, and dorsal striatum. Behav Neurosci 107:3-22.

McDonald RJ, White NM (1994) Parallel information processing in the water maze: evidence for independent memory systems involving dorsal striatum and hippocampus. Behav Neural Biol 61:260-270.

McDonald RJ, Hong NS (2004) A dissociation of dorso-lateral striatum and amygdala function on the same stimulus-response habit task. Neuroscience 124:507-513.

McEntee WJ, Mair RG (1990) The Korsakoff syndrome: a neurochemical perspective. Trends Neurosci 13:340-344.

Meibach RC, Siegel A (1977) Thalamic projections of the hippocampal formation: evidence for an alternate pathway involving the internal capsule. Brain Res 134:1-12.

Mennemeier M, Fennell E, Valenstein E, Heilman KM (1992) Contributions of the left intralaminar and medial thalamic nuclei to memory. Comparisons and report of a case. Arch Neurol 49:1050-1058.

Mennemeier M, Crosson B, Williamson DJ, Nadeau SE, Fennell E, Valenstein E, Heilman KM (1997) Tapping, talking and the thalamus: possible influence of the intralaminar nuclei on basal ganglia function. Neuropsychologia 35:183-193.

Meunier M, Bachevalier J, Mishkin M, Murray EA. (1993) Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. J Neurosci 13:5418-32.

M'Harzi M, Jarrard LE, Willig F, Palacios A, Delacour J (1991) Selective fimbria and thalamic lesions differentially impair forms of working memory in rats. Behav Neural Biol 56:221-239.

Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. Annu Rev Neurosci 24:167-202.

Milner B, Petrides M, Smith ML (1985) Frontal lobes and the temporal organization of memory.Hum Neurobiol. 4:137-42

Mitchell AS (2001) Scopolamine Infusions to the Anteroventral Thalamic Nucleus: Effects on spatial working memory in rats. Christchurch: University of Canterbury.

Mitchell AS, Dalrymple-Alford JC, Christie MA (2002) Spatial working memory and the brainstem cholinergic innervation to the anterior thalamus. J Neurosci 22:1922-1928.

Mitchell JB, Laiacona J (1998) The medial frontal cortex and temporal memory: tests using spontaneous exploratory behaviour in the rat. Behav Brain Res 97:107-113.

Mizumori SJ, Leutgeb S (2001) Directing place representation in the hippocampus. Rev Neurosci 12:347-63

Mizumori SJ, Miya DY, Ward KE (1994) Reversible inactivation of the lateral dorsal thalamus disrupts hippocampal place representation and impairs spatial learning. Brain Res 644:168-74.

Mizumori SJ, Williams JD (1993) Directionally selective mnemonic properties of neurons in the lateral dorsal nucleus of the thalamus of rats. J Neurosci 13:4015-4028.

Mogenson GJ, Jones DL, Yim CY (1980) From motivation to action: functional interface between the limbic system and the motor system. Prog Neurobiol 14:69-97.

Montagna P, Gambetti P, Cortelli P, Lugaresi E (2003) Familial and sporadic fatal insomnia. Lancet Neurol 2:167-176.

Moran JP, Dalrymple-Alford JC (2003) Perirhinal cortex and anterior thalamic lesions: comparative effects on learning and memory. Behav Neurosci 117:1326-1341.

Morris RG (2001) Episodic-like memory in animals: psychological criteria, neural mechanisms and the value of episodic-like tasks to investigate animal models of neurodegenerative disease. Philos Trans R Soc Lond B Biol Sci 356:1453-1465.

Morris RG, Garrud P, Rawlins JN, O'Keefe J (1982) Place navigation impaired in rats with hippocampal lesions. Nature 297:681-683.

Muir JL, Bussey TJ, Everitt BJ, Robbins TW (1996) Dissociable effects of AMPA-induced lesions of the vertical limb diagonal band of Broca on performance of the 5-choice serial reaction time task and on acquisition of a conditional visual discrimination. Behav Brain Res 82:31-44.

Muller RU, Ranck JB Jr, Taube JS (1996) Head direction cells: properties and functional significance. Curr Opin Neurobiol 6:196-206.

Mumby DG, Pinel JP (1994) Rhinal cortex lesions and object recognition in rats. Behav Neurosci 108:11-18.

Mumby DG, Cameli L, Glenn MJ (1999) Impaired allocentric spatial working memory and intact retrograde memory after thalamic damage caused by thiamine deficiency in rats. Behav Neurosci 113:42-50.

Mumby DG, Mana MJ, Pinel JP, David E, Banks K (1995) Pyrithiamine-induced thiamine deficiency impairs object recognition in rats. Behav Neurosci 109:1209-1214.

Murray EA, Mishkin M (1998) Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. J Neurosci 18:6568-82.

Murray EA, Mishkin M (1986) Visual recognition in monkeys following rhinal cortical ablations combined with either amygdalectomy or hippocampectomy. J Neurosci 6:1991-2003.

Neafsey EJ, Terreberry RR, Hurley KM, Ruit KG, Frysztak RJ (1993) Anterior Cingulate Cortex in Rodents: Connections, visceral control functions, and implications for emotion. In: Neurobiology of Cingulate Cortex and Limbic Thalamus: A comprehensive handbook. (Vogt BA, Gabriel M, eds). Boston: Birkhauser.

Neave N, Sahgal A, Aggleton JP (1993) Lack of effect of dorsomedial thalamic lesions on automated tests of spatial memory in the rat. Behav Brain Res 55:39-49.

Negyessy L, Hamori J, Bentivoglio M (1998) Contralateral cortical projection to the mediodorsal thalamic nucleus: originand synaptic organization in the rat. Neuroscience. 84:741-53.

Nilsson OG, Shapiro ML, Gage FH, Olton DS, Bjorklund A (1987) Spatial learning and memory following fimbria-fornix transection and grafting of fetal septal neurons to the hippocampus. Exp Brain Res. 67:195-215

Oda S (1997) Ultrastructure and distribution of corticothalamic fiber terminals from the posterior cingulate cortex and the presubiculum to the anteroventral thalamic nucleus of the rat. Brain Res Bull 42:485-91.

O'Keefe J, Nadel L (1978) The hippocampus as a cognitive map. Oxford University Press

Olton DS (1979) Mazes, maps, and memory. Am Psychol 34:583-596.

Olton DS (1983) The use of animal models to evaluate the effects of neurotoxins on cognitive processes. Neurobehav Toxicol Teratol. 5:635-40

Olton DS, Papas BC (1979) Spatial memory and hippocampal function. Neuropsychologia 17:669-682.

O'Mara SM, Commins S, Anderson M, Gigg J (2001) The subiculum: a review of form, physiology and function. Prog Neurobiol 64:129-55.

Oyoshi T, Nishijo H, Asakura T, Takamura Y, Ono T (1996) Emotional and behavioral correlates of mediodorsal thalamic neurons during associative learning in rats. J Neurosci 16:5812-29.

Packard MG, Cahill L, McGaugh JL (1994) Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes. Proc Natl Acad Sci U S A 91:8477-8481.

Packard MG, Knowlton BJ (2002) Learning and memory functions of the Basal Ganglia. Annu Rev Neurosci 25:563-593.

Packard MG, McGaugh JL (1996) Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. Neurobiol Learn Mem 65:65-72.

Packard MG, Teather LA (1997) Double dissociation of hippocampal and dorsal-striatal memory systems by posttraining intracerebral injections of 2-amino-5-phosphonopentanoic acid. Behav Neurosci 111:543-551.

Paller KA, Acharya A, Richardson BC, Plaisant O, Shimamura AP, Reed BR, Jagust JA (1997) Functional neuroimaging of cortical dysfunction in alcoholic Korskaoff syndrome. J Cog Neurosci 9:277-293.

Pardo JV, Pardo PJ, Janer KW, Raichle ME (1990) The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. Proc Natl Acad Sci U S A 87:256-9.

Parker A (1999) Memory systems, frontal cortex, and the hippocampal axis. Behav Brain Sci 22:464-465.

Parker A, Eacott MJ, Gaffan D (1997) The recognition memory deficit caused by mediodorsal thalamic lesion in non-human primates: a comparison with rhinal cortex lesion. Eur J Neurosci 9:2423-2431.

Parker A, Gaffan D (1997) The effect of anterior thalamic and cingulate cortex lesions on object-in-place memory in monkeys. Neuropsychologia 35:1093-1102.

Parkin AJ, Rees JE, Hunkin NM, Rose PE (1994) Impairment of memory following discrete thalamic infarction. Neuropsychologia 32:39-51.

Paxinos G, Watson C (1998) The Rat Brain in Stereotaxic Coordinates, 4th Ed. San Diego: Academic Press, Inc.

Peinado-Manzano MA, Pozo-Garcia R (1991) The role of different nuclei of the thalamus in processing episodic information. Behav Brain Res 45:17-27.

Peinado-Manzano MA, Pozo-Garcia R (1996) Retrograde amnesia in rats with dorsomedial thalamic damage. Behav Brain Res 80:177-184.

Phillips RG, LeDoux JE (1992) Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci. 106:274-85

Pitkanen A (2000) Connectivity of the rat amygdaloid complex. In: The Amygdala, 2nd Ed. Edition (Aggleton JP, ed). New York: Oxford University Press.

Porter MC, Koch J, Mair RG (2001) Effects of reversible inactivation of thalamo-striatal circuitry on delayed matching trained with retractable levers. Behav Brain Res 119:61-69.

Price JL, ed (1995) Thalamus, 2nd Edition. Sydney: Academic Press, Inc.

Ragozzino ME, Kesner RP (1998) The effects of muscarinic cholinergic receptor blockade in the rat anterior cingulate and Prelimbic/Infralimbic cortices on spatial working memory. Neurobiol Learn Mem 69:241-257.

Ragozzino ME, Kesner RP (1999) The role of the agranular insular cortex in working memory for food reward value and allocentric space in rats. Behav Brain Res 98:103-112.

Ragozzino ME, Kesner RP (2001) The role of rat dorsomedial prefrontal cortex in working memory for egocentric responses. Neurosci Lett 308:145-148.

Ragozzino ME, Adams S, Kesner RP (1998) Differential involvement of the dorsal anterior cingulate and prelimbic-infralimbic areas of the rodent prefrontal cortex in spatial working memory. Behav Neurosci 112:293-303.

Ragozzino ME, Detrick S, Kesner RP (1999) Involvement of the prelimbic-infralimbic areas of the rodent prefrontal cortex in behavioral flexibility for place and response learning. J Neurosci 19:4585-4594.

Ragozzino ME, Detrick S, Kesner RP (2002) The effects of prelimbic and infralimbic lesions on working memory for visual objects in rats. Neurobiol Learn Mem 77:29-43.

Reardon F, Mitrofanis J (2000) Organisation of the amygdalo-thalamic pathways in rats. Anat Embryol (Berl). 201:75-84.

Reed LJ, Lasserson D, Marsden P, Stanhope N, Stevens T, Bello F, Kingsley D, Colchester A, Kopelman MD (2003) FDG-PET findings in the Wernicke-Korsakoff syndrome. Cortex 39:1027-1045.

Rempel-Clower NL, Zola SM, Squire LR, Amaral DG (1996) Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. J Neurosci 16:5233-5255.

Robbins TW, Everitt BJ (1996) Neurobehavioural mechanisms of reward and motivation. Curr Opin Neurobiol. 6:228-36.

Russchen FT, Amaral DG, Price JL (1987) The afferent input to the magnocellular division of the mediodorsal thalamic nucleus in the monkey, Macaca fascicularis. J Comp Neurol 256:175-210.

Saint-Cyr JA (2003) Neuropsychology for movement disorders neurosurgery. Can J Neurol Sci 30 Suppl 1:S83-93.

Santin LJ, Rubio S, Begega A, Arias JL (1999) Effects of mammillary body lesions on spatial reference and working memory tasks. Behav Brain Res 102:137-150.

Satoh K, Fibiger HC (1986) Cholinergic neurons of the laterodorsal tegmental nucleus: efferent and afferent connections. J Comp Neurol. 253:277-302

Savage LM, Castillo R, Langlais PJ (1998) Effects of lesions of thalamic intralaminar and midline nuclei and internal medullary lamina on spatial memory and object discrimination. Behav Neurosci 112:1339-1352.

Savage LM, Pitkin SR, Careri JM (1999a) Memory enhancement in aged rats: the differential outcomes effect. Dev Psychobiol 35:318-327.

Savage LM, Pitkin SR, Knitowski KM (1999b) Rats exposed to acute pyrithiamine-induced thiamine deficiency are more sensitive to the amnestic effects of scopolamine and MK-801: examination of working memory, response selection, and reinforcement contingencies. Behav Brain Res 104:13-26.

Savage LM, Sweet AJ, Castillo R, Langlais PJ (1997) The effects of lesions to thalamic lateral internal medullary lamina and posterior nuclei on learning, memory and habituation in the rat. Behav Brain Res 82:133-147.

Schacter D (1987) Implicit expressions of memory in organic amnesia: learning of new facts and associations. Hum Neurobiol. 6:107-18

Schmahmann JD (2003) Vascular syndromes of the thalamus. Stroke 34:2264-2278.

Schroth G, Naegele T, Klose U, Mann K, Petersen D (1988) Reversible brain shrinkage in abstinent alcoholics, measured by MRI. Neuroradiology 30:385-389.

Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. J Neurochem 20:11-21.

Scoville WB, Milner B (2000) Loss of recent memory after bilateral hippocampal lesions. 1957. J Neuropsychiatry Clin Neurosci 12:103-113.

Seki M, Zyo K (1984) Anterior thalamic afferents from the mamillary body and the limbic cortex in the rat. J Comp Neurol 229:242-56.

Selden NR, Gitelman DR, Salamon-Murayama N, Parrish TB, Mesulam MM (1998) Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain. Brain. 121:2249-57

Sharp PE, Blair HT, Cho J (2001) The anatomical and computational basis of the rat head-direction cell signal. Trends Neurosci 24:289-94.

Shi CJ, Cassell MD (1998) Cortical, thalamic, and amygdaloid connections of the anterior and posterior insular cortices. J Comp Neurol 399:440-68

Shibata H (1992) Topographic organization of subcortical projections to the anterior thalamic nuclei in the rat. J Comp Neurol 323:117-127.

Shibata H (1993a) Direct projections from the anterior thalamic nuclei to the retrohippocampal region in the rat. J Comp Neurol 337:431-445.

Shibata H (1993b) Efferent projections from the anterior thalamic nuclei to the cingulate cortex in the rat. J Comp Neurol 330:533-542.

Shibata H (1998) Organization of projections of rat retrosplenial cortex to the anterior thalamic nuclei. Eur J Neurosci 10:3210-3219.

Shibata H, Kato A (1993) Topographic relationship between anteromedial thalamic nucleus neurons and their cortical terminal fields in the rat. Neurosci Res 17:63-69.

Shuren JE, Jacobs DH, Heilman KM (1997) Diencephalic temporal order amnesia. J Neurol Neurosurg Psychiatry 62:163-168.

Shute CC, Lewis PR (1967) The ascending cholinergic reticular system: neocortical, olfactory andsubcortical projections. Brain. 90:497-520

Sikes RW, Vogt BA (1987) Afferent connections of anterior thalamus in rats: sources and association with muscarinic acetylcholine receptors. J Comp Neurol 256:538-551.

Snitz BE, Hellinger A, Daum I (2002) Impaired processing of affective prosody in Korsakoff's syndrome. Cortex 38:797-803.
Spencer MD, Knight RS, Will RG (2002) First hundred cases of variant Creutzfeldt-Jakob disease: retrospective case note review of early psychiatric and neurological features. Bmj 324:1479-1482.
Spiegler BJ, Mishkin M (1981) Evidence for the sequential participation of inferior temporal cortex and amygdala in the acquisition of stimulus-reward associations. Behav Brain Res 3:303-317.
Squire LR (1982) The neuropsychology of human memory. Annu Rev Neurosci 5:241-273.
Squire LR (1987) Memory and Brain. New York: Oxford University Press.
Squire LR (1992) Encyclopedia of Learning and Memory. New York: Macmillan
Squire LR (1994) In Memory Systems. DL Schacter & E Tulving Eds. MIT Press
Squire LR, Zola-Morgan S (1991) The medial temporal lobe memory system. Science 253:1380-1386.
Squire LR, Knowlton B, Musen G (1993) The structure and organization of memory. Annu Rev Psychol 44:453-495.
Steckler T, Inglis W, Winn P, Sahgal A (1994) The pedunculopontine tegmental nucleus: a role in cognitive processes? Brain Res Brain Res Rev 19:298-318.
Steriade M, Dossi RC, Nunez A (1991) Network modulation of a slow intrinsic oscillation of cat thalamocortical neurons implicated in sleep delta waves: cortically induced synchronization and brainstem cholinergic suppression. J Neurosci. 11:3200-17
Stokes KA, Best PJ (1988) Mediodorsal thalamic lesions impair radial maze performance in the rat. Behav Neurosci 102:294-300.
Stokes KA, Best PJ (1990a) Response biases do not underlie the radial maze deficit in rats with mediodorsal thalamus lesions. Behav Neural Biol 53:334-345.
Stokes KA, Best PJ (1990b) Mediodorsal thalamic lesions impair "reference" and "working" memory in rats. Physiol Behav 47:471-476.
Sutherland RJ, Rodriguez AJ (1989) The role of the fornix/fimbria and some related subcortical structures in place learning and memory. Behav Brain Res 32:265-277.
Suzuki WA, Zola-Morgan S, Squire LR, Amaral DG (1983) Lesions of the perirhinal and parahippocampal cortices in the monkey produce long-lasting memory impairment in the visual and tactual modalities. J Neurosci. 13:2430-51.
Swanson LW, Cowan WM (1977) An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat. J Comp Neurol 172:49-84.
Swanson LW, Kohler C (1987) Anatomical evidence for direct projections from the entorhinal area to the entire cortical mantle in the rat. J Neurosci 6:3010-23.
Swanson LW, Sawchenko PE, Cowan WM (1981) Evidence for collateral projections by neurons in Ammon's horn, the dentate gyrus, and the subiculum: a multiple retrograde labeling study in the rat. J Neurosci 1:548-559.
Sziklas V, Petrides M (1999) The effects of lesions to the anterior thalamic nuclei on object-place associations in rats. Eur J Neurosci 11:559-566.
Takagishi M, Chiba T (1991) Efferent projections of the infralimbic (area 25) region of the medial prefrontal cortex in the rat: an anterograde tracer PHA-L study. Brain Res 566:26-39.
Tanji K, Suzuki K, Fujii T, Higano S, Yamadori A (2003) A case of frontal network amnesia. J Neurol Neurosurg Psychiatry 74:106-9.

Taube JS (1998) Head direction cells and the neurophysiological basis for a sense of direction. Prog Neurobiol 55:225-56.

Tekin S, Cummings JL (2002) Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. J Psychosom Res 53:647-654.

Temple CM, Richardson P (2004) Developmental amnesia: a new pattern of dissociation with intact episodic memory. Neuropsychologia 42:764-781.

Tulving E, Markowitsch HJ (1998) Episodic and declarative memory: role of the hippocampus. Hippocampus 8:198-204.

Uylings HB, van Eden CG (1990) Qualitative and quantitative comparison of the prefrontal cortex in rat and in primates, including humans. Prog Brain Res 85:31-62.

Uylings HB, Groenewegen HJ, Kolb B (2003) Do rats have a prefrontal cortex? Behav Brain Res 146:3-17.

Van der Werf YD, Jolles J, Witter MP, Uylings HB (2003a) Contributions of thalamic nuclei to declarative memory functioning. Cortex 39:1047-1062.

Van der Werf YD, Scheltens P, Lindeboom J, Witter MP, Uylings HB, Jolles J (2003b) Deficits of memory, executive functioning and attention following infarction in the thalamus; a study of 22 cases with localised lesions. Neuropsychologia 41:1330-1344.

Van der Werf YD, Witter MP, Groenewegen HJ (2002) The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. Brain Res Brain Res Rev 39:107-140.

Van der Werf YD, Witter MP, Uylings HB, Jolles J (2000) Neuropsychology of infarctions in the thalamus: a review. Neuropsychologia 38:613-627.

Van Der Werf YD, Weerts JG, Jolles J, Witter MP, Lindeboom J, Scheltens P (1999) Neuropsychological correlates of a right unilateral lacunar thalamic infarction. J Neurol Neurosurg Psychiatry 66:36-42.

van Groen T, Wyss JM (1990a) Connections of the retrosplenial granular a cortex in the rat. J Comp Neurol 300:593-606.

van Groen T, Wyss JM (1990b) The postsubicular cortex in the rat: characterization of the fourth region of the subicular cortex and its connections. Brain Res 529:165-177.

van Groen T, Wyss JM (1990c) The connections of presubiculum and parasubiculum in the rat. Brain Res 518:227-243.

van Groen T, Wyss JM (1992a) Connections of the retrosplenial dysgranular cortex in the rat. J Comp Neurol 315:200-216.

van Groen T, Wyss JM (1992b) Projections from the laterodorsal nucleus of the thalamus to the limbic and visual cortices in the rat. J Comp Neurol 324:427-448.

van Groen T, Wyss JM (1995) Projections from the anterodorsal and anteroventral nucleus of the thalamus to the limbic cortex in the rat. J Comp Neurol 358:584-604.

van Groen T, Kadish I, Wyss JM (1999) Efferent connections of the anteromedial nucleus of the thalamus of the rat. Brain Res Brain Res Rev 30:1-26.

van Groen T, Kadish I, Wyss JM (2002a) The role of the laterodorsal nucleus of the thalamus in spatial learning and memory in the rat. Behav Brain Res 136:329-337.

van Groen T, Kadish I, Michael Wyss J (2002b) Role of the anterodorsal and anteroventral nuclei of the thalamus in spatial memory in the rat. Behav Brain Res 132:19-28.

Vann SD, Aggleton JP (2002) Extensive cytotoxic lesions of the rat retrosplenial cortex reveal consistent deficits on tasks that tax allocentric spatial memory. Behav Neurosci 116:85-94.

Vann SD, Aggleton JP (2003) Evidence of a spatial encoding deficit in rats with lesions of the mammillary bodies or mammillothalamic tract. J Neurosci 23:3506-3514.

Vann SD, Brown MW, Aggleton JP (2000a) Fos expression in the rostral thalamic nuclei and associated cortical regions in response to different spatial memory tests. Neuroscience 101:983-991.

Vann SD, Brown MW, Erichsen JT, Aggleton JP (2000b) Using fos imaging in the rat to reveal the anatomical extent of the disruptive effects of fornix lesions. J Neurosci 20:8144-8152.

Vann SD, Wilton KLA, Muir JL, Aggleton JP (2003) Testing the importance of the caudal retrosplenial cortex for spatial memory in rats. Behav Brain Res 140:107-118.

Vargha-Khadem F, Gadian DG, Watkins KE, Connelly A, Van Paesschen W, Mishkin M (1997) Differential effects of early hippocampal pathology on episodic and semantic memory. Science 277:376-380.

Vargha-Khadem F, Salmond CH, Watkins KE, Friston KJ, Gadian DG, Mishkin M (2003) Developmental amnesia: effect of age at injury. Proc Natl Acad Sci U S A 100:10055-10060.

Vertes RP (2002) Analysis of projections from the medial prefrontal cortex to the thalamus in the rat, with emphasis on nucleus reuniens. J Comp Neurol 442:163-187.

Vertes RP (2004) Differential projections of the infralimbic and prelimbic cortex in the rat. Synapse 51:32-58.

Vertes RP, Kocsis B (1997) Brainstem-diencephalo-septohippocampal systems controlling the theta rhythm of the hippocampus. Neuroscience 81:893-926.

Vertes RP, Albo Z, Viana Di Prisco G (2001) Theta-rhythmically firing neurons in the anterior thalamus: implications for mnemonic functions of Papez's circuit. Neuroscience 104:619-25.

Victor M, Adams RD, Collins GH (1971) The Wernicke-Korsakoff syndrome. A clinical and pathological study of 245 patients, 82 with post-mortem examinations. Contemp Neurol Ser 7:1-206.

Victor M, Adams RD, Collins GH (1989) The Wernicke-Korsakoff syndrome and related neurological disorders due to alcoholism and malnutrition. 2nd edition, F.A. Davis

Visser PJ, Krabbendam L, Verhey FR, Hofman PA, Verhoeven WM, Tuinier S, Wester A, Den Berg YW, Goessens LF, Werf YD, Jolles J (1999) Brain correlates of memory dysfunction in alcoholic Korsakoff's syndrome. J Neurol Neurosurg Psychiatry 67:774-778.

von Cramon DY, Hebel N, Schuri U (1985) A contribution to the anatomical basis of thalamic amnesia. Brain 108:993-1008.

Warburton EC, Aggleton JP (1999) Differential deficits in the Morris water maze following cytotoxic lesions of the anterior thalamus and fornix transection. Behav Brain Res 98:27-38.

Warburton EC, Baird AL, Aggleton JP (1997) Assessing the magnitude of the allocentric spatial deficit associated with complete loss of the anterior thalamic nuclei in rats. Behav Brain Res 87:223-232.

Warburton EC, Morgan A, Baird AL, Muir JL, Aggleton JP (1999) Does pretraining spare the spatial deficit associated with anterior thalamic damage in rats? Behav Neurosci 113:956-967.

Warburton EC, Baird AL, Morgan A, Muir JL, Aggleton JP (2000) Disconnecting hippocampal projections to the anterior thalamus produces deficits on tests of spatial memory in rats. Eur J Neurosci 12:1714-1726.

Warburton EC, Baird A, Morgan A, Muir JL, Aggleton JP (2001) The conjoint importance of the hippocampus and anterior thalamic nuclei for allocentric spatial learning: evidence from a disconnection study in the rat. J Neurosci 21:7323-7330.

Ward-Robinson J, Wilton LA, Muir JL, Honey RC, Vann SD, Aggleton JP (2002) Sensory preconditioning in rats with lesions of the anterior thalamic nuclei: evidence for intact nonspatial 'relational' processing. Behav Brain Res 133:125-133.

White NM (1989) A functional hypothesis concerning the striatal matrix and patches: mediation of S-R memory and reward. Life Sci 45:1943-1957.

White NM, McDonald RJ (2002) Multiple parallel memory systems in the brain of the rat. Neurobiol Learn Mem 77:125-184.

Wilton LA, Baird AL, Muir JL, Aggleton JP (2001a) Excitotoxic lesions of the rostral thalamic reticular nucleus do not affect the performance of spatial learning and memory tasks in the rat. Behav Brain Res 120:177-187.

Wilton LA, Baird AL, Muir JL, Honey RC, Aggleton JP (2001b) Loss of the thalamic nuclei for "head direction" impairs performance on spatial memory tasks in rats. Behav Neurosci 115:861-869.

Winn P, Brown VJ, Inglis WL (1997) On the relationships between the striatum and the pedunculopontine tegmental nucleus. Crit Rev Neurobiol 11:241-261.

Winocur G (1985) The hippocampus and thalamus: their roles in short- and long-term memory and the effects of interference. Behav Brain Res 16:135-152.

Witter MP, Groenewegen HJ (1990) The subiculum: cytoarchitectonically a simple structure, but hodologically complex. Prog Brain Res 83:47-58.

Witter MP, Groenewegen HJ, Lopes da Silva FH, Lohman AH (1989) Functional organization of the extrinsic and intrinsic circuitry of the parahippocampal region. Prog Neurobiol 33:161-253.

Witter MP, Van der Werf YD (1999) The medial dorsal nucleus of the thalamus is not part of a hippocampal-thalamic memory system. Behav Brain Sci 22: 467-468

Wyss JM, Van Groen T (1992) Connections between the retrosplenial cortex and the hippocampal formation in the rat: a review. Hippocampus 2:1-11.

Young AW, Aggleton JP, Hellawell DJ, Johnson M, Broks P, Hanley JR (1995) Face processing impairments after amygdalotomy. Brain 118:15-24.

Young HL, Stevens AA, Converse E, Mair RG (1996) A comparison of temporal decay in place memory tasks in rats (Rattus norvegicus) with lesions affecting thalamus, frontal cortex, or the hippocampal system. Behav Neurosci 110:1244-1260.

Zhang Y, Burk JA, Glode BM, Mair RG (1998) Effects of thalamic and olfactory cortical lesions on continuous olfactory delayed nonmatching-to-sample and olfactory discrimination in rats (Rattus norvegicus). Behav Neurosci 112:39-53.

Zhu XO, Brown MW, McCabe BJ, Aggleton JP (1995) Effects of the novelty or familiarity of visual stimuli on the expression of the immediate early gene c-fos in rat brain. Neuroscience 69:821-9.

Zola-Morgan S, Cohen N, Squire LR (1983) Recall of remote episodic memory in amnesia. Neuropsychologia. 21:487-500

Zola-Morgan S, Squire LR (1985) Amnesia in monkeys after lesions of the mediodorsal nucleus of the thalamus. Ann Neurol 17:558-564.

Zola-Morgan S, Squire LR (1993) Neuroanatomy of memory. Annu Rev Neurosci 16:547-563.

Zola-Morgan S, Squire LR, Amaral DG (1989) Lesions of the hippocampal formation but not lesions of the fornix or the mammillary nuclei produce long-lasting memory impairment in monkeys. J Neurosci 9:898-913.

Zola-Morgan S, Squire LR, Ramus SJ (1994) Severity of memory impairment in monkeys as a function of locus and extent of damage within the medial temporal lobe memory system. Hippocampus 4:483-495.

Zola-Morgan S, Squire LR, Rempel NL, Clower RP, Amaral DG (1992) Enduring memory impairment in monkeys after ischemic damage to the hippocampus. J Neurosci 12:2582-2596.

Zoppelt D, Koch B, Schwarz M, Daum I (2003) Involvement of the mediodorsal thalamic nucleus in mediating recollection and familiarity. Neuropsychologia 41:1160-1170.

Appendix A

The configurations for the 8 baited arms / 2 never-baited arms used in the 12-arm radial maze task of Experiment One (Chapter 7).

Configuration	Baited Open Arms	Never-Baited Open Arms	Never-Baited Blocked Arms
1	2,4,5,6,8,9,11,12	1, 7	3, 10
2	2,4,5,6,8,9,11,12	7, 10	1, 3
3	2,4,5,6,8,9,11,12	1, 10	3, 7
4	2,4,5,6,8,9,11,12	3, 7	1, 10
5	1,3,4,6,7,8,10,11	2, 5	9, 12
6	1,3,4,6,7,8,10,11	5, 9	2, 12
7	1,3,4,6,7,8,10,11	9, 12	2, 5
8	1,3,4,6,7,8,10,11	2, 12	5, 9
9	1,2,3,5,7,9,10,12	8, 11	4, 6
10	1,2,3,5,7,9,10,12	4, 6	8, 11
11	1,2,3,5,7,9,10,12	6, 11	4, 8
12	1,2,3,5,7,9,10,12	4, 8	6, 11

The configurations were randomised across the 47 rats that were tested in the task.